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Predictors of food sensitization in children and adults across Europe

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Abstract: BACKGROUND: The geographical variation and temporal increase in the prevalence of food sensitization (FS) suggest environmental influences. OBJECTIVE: To investigate how environment, infant diet, and demographic characteristics, are associated with FS in children and adults, focusing on early-life exposures. METHODS: Data on childhood and adult environmental exposures (including, among others, sibship size, daycare, pets, farm environment, and smoking), infant diet (including breast-feeding and timing of introduction to infant formula and solids), and demographic characteristics were collected from 2196 school-age children and 2185 adults completing an extensive questionnaire and blood sampling in the cross-sectional pan-European EuroPrevall project. Multivariable logistic regression was applied to determine associations between the predictor variables and sensitization to foods commonly implicated in food allergy (specific IgE $0.35 \text{ kU}_A/\text{L}$). Secondary outcomes were inhalant sensitization and primary (non-cross-reactive) FS. RESULTS: Dog ownership in early childhood was inversely associated with childhood FS (odds ratio, 0.65; 95% CI, 0.48-0.90), as was higher gestational age at delivery (odds ratio, 0.93 [95% CI, 0.87-0.99] per week increase in age). Lower age and male sex were associated with a higher prevalence of adult FS (odds ratio, 0.97 [95% CI, 0.96-0.98] per year increase in age, and 1.39 [95% CI, 1.12-1.71] for male sex). No statistically significant associations were found between other evaluated environmental determinants and childhood or adult FS, nor between infant diet and childhood FS, although early introduction of solids did show a trend toward prevention of FS. CONCLUSIONS: Dog ownership seems to protect against childhood FS, but independent effects of other currently conceived environmental and infant dietary determinants on FS in childhood or adulthood could not be confirmed.

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Predictors of Food Sensitization in Children and Adults Across Europe



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What is already known about this topic? Prevalence of food sensitization (FS) varies considerably across Europe, and is reported to be on the rise. Environmental influences are likely, but studies investigating currently conceived environmental predictors for FS are lacking.

What does this article add to our knowledge? This is the first study evaluating the main postulated environmental risk factors for FS, using a standardized approach in both children and adults across Europe. Mutually adjusted associations between primarily early-life exposures and FS are revealed.

How does this study impact current management guidelines? Dog ownership appears to protect against childhood FS, but other environmental factors appear to have (more) limited impact on the prevalence of FS in European children and adults.

BACKGROUND: The geographical variation and temporal increase in the prevalence of food sensitization (FS) suggest environmental influences.

OBJECTIVE: To investigate how environment, infant diet, and demographic characteristics, are associated with FS in children and adults, focusing on early-life exposures.

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Abbreviations used

FA- Food allergy

FS- Food sensitization

IS- Inhalant sensitization

OR- Odds ratio

METHODS: Data on childhood and adult environmental exposures (including, among others, sibship size, day care, pets, farm environment, and smoking), infant diet (including breastfeeding and timing of introduction to infant formula and solids), and demographic characteristics were collected from 2196 school-age children and 2185 adults completing an extensive questionnaire and blood sampling in the cross-sectional pan-European EuroPrevall project. Multivariable logistic regression was applied to determine associations between the predictor variables and sensitization to foods commonly implicated in food allergy (specific IgE ≥ 0.35 kU_A/L). Secondary outcomes were inhalant sensitization and primary (non-cross-reactive) FS. **RESULTS:** Dog ownership in early childhood was inversely associated with childhood FS (odds ratio, 0.65; 95% CI, 0.48-0.90), as was higher gestational age at delivery (odds ratio, 0.93 [95% CI, 0.87-0.99] per week increase in age). Lower age and male sex were associated with a higher prevalence of adult FS (odds ratio, 0.97 [95% CI, 0.96-0.98] per year increase in age, and 1.39 [95% CI, 1.12-1.71] for male sex). No statistically significant associations were found between other evaluated environmental determinants and childhood or adult FS, nor between infant diet and childhood FS, although early introduction of solids did show a trend toward prevention of FS. **CONCLUSIONS:** Dog ownership seems to protect against childhood FS, but independent effects of other currently conceived environmental and infant dietary determinants on FS in childhood or adulthood could not be confirmed. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2020;8:3074-83)

Key words: Food sensitization; Food allergy; Inhalant sensitization; Predictors; Risk factors; Early-life exposures; Environment; Infant diet; Dog; Europe

INTRODUCTION

Prevalence estimates of IgE sensitization to foods range from 11% to 29% in 7- to 10-year-old children and from 7% to 24% in adults across various European countries.^{1,2} Several studies indicate that the prevalence of food sensitization (FS) in children and adults is rising.³⁻⁷ The geographical variation in the prevalence of FS in children and adults of comparable genetic background, and the proposed increase in FS prevalence over time, suggest an effect of environmental factors.⁸

Although FS does not invariably lead to food allergy (FA), it is a prerequisite, and an objective end point that can feasibly be obtained for multiple foods in a large group of participants. Studies investigating environmental predictors for FS are scarce. Some previous studies report a protective effect of certain environmental determinants on FS in children, such as younger maternal age at delivery,⁹ higher number of previous pregnancies,¹⁰ exposure to a farm environment,^{10,11} or having childhood

pets (dogs or cats).¹¹ Determinants related to infant diet also may be relevant. Vitamin D insufficiency and late introduction of solid foods, for example, have been associated with an increased likelihood of FS.¹²⁻¹⁴ In adults, a link between the use of antacids and increased FS has been proposed.¹⁵ Most studies in adults, however, tend to focus on inhalant sensitization (IS) or other atopic diseases as outcomes.^{16,17} As part of the European Community Respiratory Health Survey, Svanes et al performed extensive analyses on the effect of a multitude of childhood environmental determinants on adult sensitization to inhalant allergens, and found a protective effect of increasing family size, bedroom sharing, and the presence of a dog in the childhood home.¹⁷ Studies on this scale, which include multiple suggested risk factors and allow for mutual adjustment, are not yet available for the outcome FS or FA. Such studies are key to helping us understand differences in prevalence and time trends between and within populations.⁸

This gap in knowledge led to the current study, in which the primary aim was to investigate how environmental, dietary, and demographic determinants are associated with sensitization to foods that are commonly consumed across Europe and frequently implicated in FA. The focus was on early-life events and exposures, and the outcome was assessed in both children and adults, using data collected from all across Europe in a standardized manner during the European Union-funded EuroPrevall project. Secondary outcomes included IS and primary (non-cross-reactive) FS, to determine whether there are differences between predictors for FS and IS, the latter of which was the focus of previous studies in adult populations.¹⁷

METHODS

Study design, setting, and subjects

A full description of the methodology of the EuroPrevall study, a cross-sectional cohort study with a case-control design nested within, is available elsewhere.¹⁸ In the current study, we included randomly sampled children (7-10 years) and adults (20-54 years) from the general population of Athens (Greece), Lodz (Poland), Madrid (Spain), Reykjavik (Iceland), Utrecht (The Netherlands), Zurich (Switzerland), and Vilnius (Lithuania), who completed phase I (a short screening questionnaire) and phase II (a detailed questionnaire, and blood sampling for detection of IgE against 24 common food allergens [termed *priority foods*] and 6 common inhalant allergens [as summarized in [Online Repository Methods on data collection](#) in this article's Online Repository at www.jaci-inpractice.org]). All phase I participants who reported symptoms to 1 or more of the 24 priority foods (cases) and a random sample of phase I participants who reported no symptoms to these foods (controls) were invited for phase II. All data were collected between 2007 and 2009 for children, with a median time interval of 5 months between phase I and II; and between 2006 and 2009 for adults, with a median time interval of 8 months. The local ethical committees of all participating centers gave approval for this study, and informed consent was obtained from all participants.

Data collection

The primary outcome, FS, was defined as positive serology (specific IgE ≥ 0.35 kU_A/L) to at least 1 of the 24 selected foods. IS was considered present if a subject was sensitized to at least 1 of the 6 selected inhalant allergens. Primary FS, defined as sensitization occurring through true plant- or animal-derived food allergens, rather than through pollen inhalant allergens cross-reacting

with plant food allergens, was determined using an allergen microarray assay (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). The overlap between the various outcome variables is depicted in [Figure E2](#) in this article's Online Repository at www.jaci-inpractice.org.

Information on determinants was extracted from answers to the EuroPrevall phase II questionnaire (see [Figures E3](#) and [E4](#) in this article's Online Repository at www.jaci-inpractice.org). In addition to the childhood environmental factors that were investigated for both adults and children, infant dietary factors were taken into account for children, and adult environmental factors for adults. Childhood environmental determinants were investigated for exposure before the age of 2 years for children and before the age of 5 years for adults. To give a complete overview, demographic factors were also assessed. More details on data collection are available in this article's Online Repository at www.jaci-inpractice.org.

Data analysis

As an initial exploration, differences between subjects with and without FS were examined using the χ^2 test for categorical variables and the 2-sample *t* test for continuous variables. Univariable logistic regression was performed to assess crude associations between each individual determinant and FS (crude odds ratios [ORs]). Multivariable logistic regression including all determinants was then applied to obtain the independent contribution of the determinants to FS (adjusted ORs). Details on missing data are available from [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org. To ensure optimal power in the multivariable analysis and potentially reduce bias, multiple imputation was performed using fully conditional specification (20 imputations, 20 iterations), for which all variables in [Table E1](#) were included as covariates. Because it is known that the prevalence of FS is variable between countries,^{1,2} all analyses were controlled for center by adding center as a categorical covariate in the model. To better understand the independent contribution of the various determinants, a stepwise approach to model building was chosen. In model I, multivariable analysis was performed with only demographic factors. In model II, childhood environmental determinants were added. In model III, infant dietary determinants were added for children, and adult environmental determinants for adults.

To observe how the association between the determinants and FS changed on adding comorbidity with overlapping pathophysiological mechanisms, we performed additional analyses. First comorbid atopy (asthma, allergic rhinitis, or atopic dermatitis, or at least 1 of these 3 diseases in first-degree relatives, or parental FA [for the pediatric population]), and then coexisting IgE sensitization to inhalant allergens, was incorporated into model III.

To evaluate whether predictors for FS differ from predictors for IS and primary FS, and enable comparison with earlier studies regarding factors associated with sensitization, we also fitted model III for these outcomes.

Analyses were conducted with SPSS version 25 (IBM Corporation, Armonk, NY). *P* values less than .05 were considered statistically significant.

RESULTS

Of the 2326 children and 2256 adults completing the phase II questionnaire, the 2196 children and 2185 adults with available food serology were evaluated in this study. There were no differences in age or sex between those subjects who did and who did not complete phase II. In subjects who did complete phase II, subjects with available serology appeared somewhat more

likely to report symptoms to (priority foods) and were more likely to be male, than subjects with missing serology results, but no other remarkable differences were observed in demographic characteristics or allergic comorbidities (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

Respectively 494 children and 441 adults were sensitized to at least 1 of the priority foods. The median age of the children was 8.9 years in both those with and without FS, and respectively 50.8% and 49.6% were males ([Table I](#)). The food-sensitized adults had a median age of 35.3 years and 49.0% were males, whereas the nonsensitized adults had a median age of 39.2 years and 41.1% were males ([Table II](#)). Data on all determinants were complete in 76.5% of the children and 82.2% of the adults; in the rest, missing values on 1 or more of the determinants were estimated by multiple imputation.

Children: Crude associations between demographic, childhood environmental, and infant dietary determinants and FS

[Table I](#) presents the results of univariable analyses in children. No significant associations between demographic factors, age, sex, and parental level of education and FS in childhood were found. Lower gestational age, lower birth weight, and shorter length at birth tended to increase the likelihood of FS ([Table I](#)). Comorbid atopy, parental FA, and IS also showed strong positive associations with FS.

Many childhood environmental factors demonstrated significant inverse associations with FS, specifically having more siblings, having older siblings, day care attendance before the age of 2 years, and having a pet dog before the age of 2 years.

Regarding dietary determinants, breast-feeding for longer than 6 months was inversely associated with FS, compared with breast-feeding for less than 6 months. Breast-feeding was not necessarily exclusive. Use of infant formula, which could be either a replacement of or complementary to breast-feeding, was positively associated with FS, especially hypoallergenic infant formula. In subjects who received infant formula, a trend was suggested where the younger infant formula was introduced, the less likely FS became. A similar trend was observed for solid food introduction.

Independent predictors of FS in children

In multivariable analyses, gestational age was the only demographic determinant that remained significantly associated with FS in childhood ([Table III](#)). The longer the pregnancy, the lower the chance of FS in the child (OR, 0.93 [95% CI, 0.87-0.99] per week of pregnancy duration). Of the childhood environmental determinants, having a pet dog before the age of 2 years was still significantly inversely associated after multivariable adjustment (OR, 0.65 [95% CI, 0.48-0.90]). Of the infant dietary determinants, use of hypoallergenic infant formula maintained a positive association with childhood FS (OR, 1.51 [95% CI, 1.06-2.15]).

Adjustment for comorbid atopy did not result in relevant changes to the associations obtained in model III (see [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org). Subsequent correction for coexisting IS resulted in male sex becoming significantly inversely associated with FS (OR, 0.64 [95% CI, 0.49-0.84]) and attenuated the associations between having a pet dog before the age of 2 years and use of hypoallergenic infant formula and FS in childhood, suggesting that

TABLE I. Characteristics of children and crude associations with FS

Variable	Sensitized (N = 494)	Not sensitized (N = 1702)	P	Crude OR (95% CI)
Demographic characteristic				
Age (y), mean \pm SD	8.97 \pm 0.98	8.88 \pm 0.96	.16	1.09 (0.98-1.21)
Sex				
Male	251 (50.8)	845 (49.6)	.65	1.05 (0.86-1.28)
Female	243 (49.2)	857 (50.4)		
Highest level of education of parents				
High	206 (41.7)	732 (43.0)	.60	0.95 (0.77-1.16)
Low	288 (58.3)	969 (57.0)		
Gestational age (wk), mean \pm SD	39.16 \pm 2.30	39.48 \pm 1.93	<.001	0.93 (0.89-0.97)
Birth weight (g), mean \pm SD	3344.27 \pm 561.28	3398.98 \pm 600.48	.07	0.98 (0.97-1.00) per 100 g
Birth length (cm), mean \pm SD	51.11 \pm 3.27	51.57 \pm 3.38	.01	0.96 (0.93-0.99)
Childhood environment				
Maternal age (y), mean \pm SD	29.75 \pm 5.19	29.67 \pm 5.54	.78	1.00 (0.98-1.02)
No. of siblings				
0	97 (19.7)	302 (17.8)	.05	Reference
1	247 (50.2)	859 (50.6)		0.90 (0.69-1.18)
2	118 (24.0)	368 (21.7)		1.00 (0.73-1.36)
3 or more	30 (6.1)	169 (10.0)		0.55 (0.35-0.86)
No. of older siblings				
0	277 (56.3)	857 (50.5)	.02	Reference
1	154 (31.3)	591 (34.8)		0.81 (0.64-1.01)
2	51 (10.4)	175 (10.4)		0.90 (0.64-1.26)
3 or more	10 (2.0)	10 (2.0)		0.41 (0.20-0.77)
Bedroom sharing with other children*	135 (27.3)	493 (29.1)	.45	0.92 (0.73-1.15)
Bedroom sharing with older children*	118 (23.9)	428 (25.2)	.56	0.93 (0.74-1.18)
Day care attendance*	175 (35.4)	698 (41.1)	.02	0.79 (0.64-0.97)
Farm environment*	2 (0.4)	8 (0.5)	>.99	0.86 (0.13-3.45)
Inner-city environment*	212 (42.9)	741 (43.5)	.81	0.97 (0.80-1.19)
Pet dog*	65 (13.2)	429 (86.8)	.01	0.67 (0.50-0.89)
Pet cat*	79 (16.0)	280 (16.5)	.80	0.97 (0.73-1.26)
Serious respiratory tract infection*	133 (26.9)	424 (24.9)	.37	1.11 (0.88-1.39)
Use of antibiotics*	296 (59.9)	1025 (60.3)	.88	0.98 (0.80-1.21)
Maternal smoking during pregnancy	63 (12.8)	253 (14.9)	.23	0.84 (0.62-1.12)
Maternal smoking since birth	149 (30.2)	528 (31.1)	.70	0.96 (0.77-1.19)
Paternal smoking since birth	201 (40.7)	710 (41.8)	.67	0.96 (0.78-1.17)
Reflux medication in last 6 mo	3 (0.6)	17 (1.0)	.42	0.61 (0.14-1.81)
Infant diet				
Vitamin D supplementation*	374 (80.4)	1324 (82.3)	.35	0.88 (0.68-1.15)
Breast-feeding duration				
Never	51 (10.4)	173 (10.3)	.07	Reference
\leq 4 mo	173 (35.3)	521 (31.1)		1.13 (0.79-1.62)
4-6 mo	80 (16.3)	237 (14.1)		1.15 (0.77-1.72)
>6 mo	186 (38.0)	745 (44.5)		0.85 (0.60-1.21)
Cow's milk infant formula	282 (57.9)	982 (58.2)	.90	0.99 (0.81-1.21)
Soy milk infant formula	38 (7.8)	110 (6.5)	.31	1.22 (0.82-1.77)
Hypoallergenic infant formula	126 (25.9)	286 (17.0)	<.001	1.71 (1.34-2.17)
Age start infant formula				
Never	91 (18.7)	430 (25.6)	.02	Reference
0-4 mo	225 (46.3)	742 (44.2)		1.43 (1.10-1.89)
4-6 mo	61 (12.6)	188 (11.2)		1.53 (1.06-2.21)
6-11 mo	81 (16.7)	253 (15.1)		1.51 (1.08-2.12)
\geq 11 mo	28 (5.8)	66 (3.9)		2.00 (1.21-3.27)

(continued)

TABLE I. (Continued)

Variable	Sensitized (N = 494)	Not sensitized (N = 1702)	P	Crude OR (95% CI)
Age of introduction of solid foods				
0-4 mo	76 (15.7)	342 (20.6)	.04	Reference
4-6 mo	226 (46.8)	738 (44.4)		1.38 (1.04-1.85)
6-11 mo	133 (27.5)	463 (27.8)		1.29 (0.95-1.78)
≥11 mo	48 (9.9)	120 (7.2)		1.80 (1.18-2.73)
Comorbid atopy	26 (5.3)	189 (11.3)	<.001	2.28 (1.52-3.55)
Parental FA	128 (29.0)	377 (24.8)	.07	1.24 (0.98-1.57)
Pollen sensitization†	325 (66.7)	178 (10.6)	<.001	16.89 (13.26-21.62)
IS overall‡	368 (75.6)	335 (20.0)	<.001	12.39 (9.78-15.78)
Center				
Zurich	93 (18.8)	211 (12.4)	<.001	2.71 (1.89-3.89)
Madrid	82 (16.6)	196 (11.5)		2.57 (1.78-3.73)
Athens	40 (8.1)	115 (6.8)		2.14 (1.36-3.33)
Utrecht	102 (20.6)	296 (17.4)		2.12 (1.50-3.00)
Lodz	83 (16.8)	370 (21.7)		1.38 (0.97-1.97)
Vilnius	30 (6.1)	121 (7.1)		1.52 (0.93-2.44)
Reykjavik	64 (13.0)	393 (23.1)		Reference

Results presented in n (%) unless otherwise specified. Bold indicates statistical significance ($P < .05$).

*Before the age of 2 y.

†IgE sensitization to birch, grass, mugwort, or parietaria.

‡IgE sensitization to pollen, cat, or house-dust mite.

reverse causality explains part of the observed associations (Table E3). The association between pet dog and FS remained significant.

Adults: Crude associations between demographic, childhood, and adult environmental determinants and FS

Table II presents the results of univariable analyses in adults. Of the demographic factors, younger age and male sex were significantly positively associated with FS, as were comorbid atopy and IS.

Analyses of childhood environmental determinants in adults showed a significant inverse association between having more siblings, sharing a bedroom with other or older children before the age of 5 years, and growing up on a farm before the age of 5 years and FS in adulthood (Table II). In contrast to the findings in children, day care attendance before the age of 5 years was shown to significantly increase the likelihood of adult FS.

Of the adult environmental determinants, ever having had a food-related occupation was associated with a lower risk of FS.

Independent predictors of FS in adults

Only the demographic factors age and sex remained significantly associated with adult FS after multivariable adjustment (Table III), yielding an OR of 0.97 (95% CI, 0.96-0.98) per year increase in age and an OR of 1.39 (95% CI, 1.12-1.71) for male sex. Multivariable analyses revealed no significant associations between childhood or adult environmental determinants and FS in adults.

Addition of comorbid atopy and subsequently IS to the model did not notably change any of the observed associations (Table E3).

Secondary outcomes: Independent predictors of sensitization to inhalant allergens and primary food allergens

Table E4 in this article's Online Repository at www.jaci-inpractice.org facilitates comparison of predictors for FS, as discussed above, with predictors of the secondary outcomes, IS and primary FS.

In children, the results pertaining to IS were generally similar to those related to FS. Noticeable exceptions were that bedroom sharing with other children before the age of 2 years and growing up in a farm environment showed stronger inverse associations with IS, the former of which reached statistical significance. Also, although sex was not associated with FS, male sex was significantly positively associated with IS. Regarding primary FS, no particular differences in predictors were found compared with overall FS.

In adults, it was noteworthy that where there were no significant associations between the childhood environmental determinants and FS in adulthood, there was a significant inverse association between growing up in a farm environment or with a pet cat before the age of 5 years and IS. Furthermore, increasing maternal age was significantly associated with a higher risk of IS. Adjustment for comorbid atopy attenuated the protective effect of cat ownership, but not that of farm or maternal age, which suggests some reverse causality in the association between cat ownership and IS.

Regarding the outcome primary FS, bedroom sharing with older children before the age of 5 years was found to be inversely associated, and smoking in adulthood significantly increased the likelihood of primary FS in adults.

DISCUSSION

Summary of findings

Until now, no study existed in which the main postulated environmental and infant dietary risk factors for FA were evaluated collectively in multivariable analysis, especially not all over

TABLE II. Characteristics of adults and crude associations with FS

Variable	Sensitized (N = 441)	Not sensitized (N = 1744)	P	Crude OR (95% CI)
Demographic characteristic				
Age (y), mean \pm SD	36.10 \pm 9.35	38.89 \pm 9.52	<.001	0.97 (0.96-0.98)
Sex				
Male	216 (49.0)	716 (41.1)	<.001	1.38 (1.12-1.70)
Female	225 (51.0)	1028 (58.9)		
Level of education				
High	285 (64.6)	1151 (66.0)	.59	0.94 (0.76-1.17)
Low	156 (35.4)	593 (34.0)		
Childhood environment				
Maternal age (y), mean \pm SD	28.60 \pm 5.59	28.03 \pm 5.90	.07	1.02 (1.00-1.03)
No. of siblings				
0	32 (7.3)	128 (7.4)	.01	Reference
1	169 (38.7)	582 (33.5)		1.16 (0.77-1.80)
2	122 (27.9)	428 (24.6)		1.14 (0.74-1.79)
3 or more	114 (26.1)	601 (34.6)		0.76 (0.50-1.19)
No. of older siblings				
0	182 (41.6)	697 (40.1)	.39	Reference
1	141 (32.3)	536 (30.8)		1.01 (0.79-1.29)
2	70 (16.0)	269 (15.5)		1.00 (0.73-1.35)
3 or more	44 (10.1)	237 (13.6)		0.71 (0.49-1.01)
Bedroom sharing with other children*	236 (53.5)	1058 (60.7)	.01	0.74 (0.60-0.92)
Bedroom sharing with older children*	134 (30.6)	650 (37.4)	.01	0.74 (0.59-0.92)
Day care attendance*	251 (58.8)	906 (53.3)	.04	1.25 (1.01-1.55)
Farm environment*	14 (3.2)	105 (6.0)	.02	0.51 (0.28-0.87)
Inner-city environment*	147 (33.3)	535 (30.7)	.28	1.13 (0.90-1.41)
Pet dog*	165 (37.4)	692 (39.7)	.38	0.91 (0.73-1.13)
Pet cat*	163 (37.0)	696 (39.9)	.26	0.88 (0.71-1.09)
Serious respiratory tract infection*	46 (11.3)	211 (13.2)	.30	0.84 (0.59-1.16)
Adult environment				
Smoking	224 (50.8)	928 (53.2)	.36	0.91 (0.74-1.12)
Food-related occupation	109 (24.7)	540 (31.0)	.01	0.73 (0.57-0.93)
Indigestion medication currently				
No or <1 \times /y	386 (87.5)	1513 (86.8)	.15	Reference
Yes, <1 \times /mo	35 (7.9)	110 (6.3)		1.25 (0.83-1.84)
Yes, <1 \times /wk	7 (1.6)	30 (1.7)		0.91 (0.37-1.98)
Yes, \geq 1 \times /wk	13 (2.9)	91 (5.2)		0.56 (0.0-0.98)
Comorbid atopy	28 (6.3)	371 (21.3)	<.001	3.99 (2.72-6.07)
Pollen sensitization [†]	340 (80.8)	287 (16.7)	<.001	20.96 (16.02-17.70)
IS overall [‡]	37 (8.8)	437 (25.4)	<.001	30.47 (21.66-44.10)
Center				
Zurich	147 (33.3)	335 (19.2)	<.001	4.88 (3.37-7.23)
Madrid	63 (14.3)	246 (14.1)		2.85 (1.86-4.41)
Athens	15 (3.4)	52 (3.0)		3.21 (1.62-6.12)
Utrecht	112 (25.4)	364 (20.9)		3.42 (2.34-5.11)
Lodz	65 (14.7)	313 (17.9)		2.31 (1.52-3.55)
Reykjavik	39 (8.8)	434 (24.9)		Reference

Results presented in n (%) unless otherwise specified. Bold indicates statistical significance ($P < .05$).

*Before the age of 5 y.

[†]IgE sensitization to birch, grass, mugwort, or parietaria.

[‡]IgE sensitization to pollen, cat, or house-dust mite.

Europe for both children and adults. The data from the Euro-Prevall project made this possible. In our study, having a pet dog before the age of 2 years was the only statistically significantly predictive early-life exposure, and it was found to be strongly associated with a decreased risk of FS in childhood. Higher

gestational age at birth was also significantly inversely associated with childhood FS. No childhood or adult environmental determinants were significantly associated with FS in adulthood, but demographic characteristics lower age and male sex did make adult FS more likely.

TABLE III. Independent predictors of FS

Variable	Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Demographic characteristic				
Age (y)	1.01 (0.91-1.13)	.85	0.97 (0.96-0.98)	<.001
Male sex	1.01 (0.82-1.25)	.92	1.39 (1.12-1.73)	<.001
High level of education*	1.02 (0.80-1.29)	.88	0.86 (0.67-1.09)	.21
Gestational age (wk)	0.93 (0.87-0.99)	.01	NA	NA
Birth weight (g)	1.00 (1.00-1.00)	.97	NA	NA
Birth length (cm)	1.01 (0.97-1.06)	.65	NA	NA
Childhood environment				
Maternal age (y)	0.99 (0.97-1.01)	.33	1.01 (0.99-1.03)	.45
No. of siblings				
1	0.86 (0.63-1.18)	.28	1.22 (0.75-1.97)	.74
2	1.09 (0.73-1.64)		1.34 (0.78-2.29)	
3 or more	0.76 (0.40-1.44)		1.35 (0.75-2.42)	
No. of older siblings				
1	0.85 (0.63-1.15)	.62	1.17 (0.85-1.62)	.74
2	1.02 (0.63-1.18)		1.21 (0.78-1.88)	
3 or more	0.77 (0.31-1.95)		1.22 (0.69-2.14)	
Bedroom sharing with other children	0.77 (0.53-1.13) [†]	.18	0.84 (0.62-1.14) [‡]	.26
Bedroom sharing with older children	1.19 (0.79-1.80) [†]	.40	0.75 (0.52-1.06) [‡]	.11
Day care attendance	0.82 (0.64-1.05) [†]	.12	1.02 (0.80-1.30) [‡]	.89
Farm environment	1.06 (0.21-5.36) [†]	.95	0.73 (0.40-1.35) [‡]	.32
Inner-city environment	0.94 (0.76-1.17) [†]	.60	1.01 (0.79-1.29) [‡]	.93
Pet dog	0.65 (0.48-0.90)[†]	.01	0.94 (0.70-1.27) [‡]	.61
Pet cat	1.04 (0.77-1.40) [†]	.79	0.87 (0.68-1.10) [‡]	.24
Serious respiratory tract infection	1.11 (0.86-1.45) [†]	.42	0.88 (0.62-1.25) [‡]	.47
Use of antibiotics	1.14 (0.89-1.45) [†]	.29	NA	NA
Maternal smoking during pregnancy	0.74 (0.51-1.08)	.12	NA	NA
Maternal smoking since birth	1.12 (0.84-1.48)	.45	NA	NA
Paternal smoking since birth	0.97 (0.77-1.22)	.78	NA	NA
Reflux medication in last 6 mo	0.61 (0.17-2.19)	.45	NA	NA
Infant diet				
Vitamin D supplementation	1.05 (0.75-1.47) [†]	.77	NA	NA
Breast-feeding duration				
≤4 mo	1.20 (0.82-1.75)	.29	NA	NA
4-6 mo	1.20 (0.75-1.94)		NA	NA
>6 mo	0.91 (0.57-1.46)		NA	NA
Cow's milk infant formula	0.85 (0.58-1.24)	.39	NA	NA
Soy milk infant formula	1.35 (0.89-2.05)	.16	NA	NA
Hypoallergenic infant formula	1.51 (1.06-2.15)	.02	NA	NA
Age start infant formula				
0-4 mo	1.02 (0.60-1.72)	.29	NA	NA
4-6 mo	1.04 (0.60-1.79)		NA	NA
6-11 mo	1.10 (0.66-1.82)		NA	NA
≥11 mo	1.79 (0.94-3.40)		NA	NA
Age introduction solid foods				
4-6 mo	1.37 (1.00-1.86)	.33	NA	NA
6-11 mo	1.22 (0.86-1.71)		NA	NA
≥11 mo	1.45 (0.93-2.27)		NA	NA
Adult environment				
Smoking	NA	NA	0.9 (0.79-1.24)	.94
Food-related occupation	NA	NA	0.83 (0.64-1.07)	.15

(continued)

TABLE III. (Continued)

Variable	Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Indigestion medication currently				
<1×/mo	NA	NA	1.30 (0.85-1.97)	.59
<1×/wk	NA	NA	1.10 (0.46-2.60)	
≥ 1×/wk	NA	NA	0.84 (0.46-1.54)	

NA, Not available.

Bold indicates statistical significance ($P < .05$). Analyses were adjusted for center.

Reference categories: “number of (older) siblings” = 0; “indigestion medication” = no or <1×/y; “breast-feeding duration” = never; “age start infant formula” = never; “age introduction solid food” = 0-4 mo.

*For children: high level of education of parents.

†Before the age of 2 y.

‡Before the age of 5 y.

Early-life exposures: Environmental determinants

The finding that having a pet dog in early childhood was inversely associated with FS consolidates existing evidence that dog ownership protects against childhood FA.^{19,21} The protective effect is thought to be the result of exposure to diverse environmental microbiota.²¹ Similarly to the adjusted OR of 0.65 (95% CI, 0.48-0.90) in the current study, Koplin et al²² reported an adjusted OR of 0.6 (95% CI, 0.3-0.8) for the association between dog ownership and challenge-proven egg, peanut, and sesame allergy in Australian infants participating in the HealthNuts study; and Von Hertzen et al¹¹ found an adjusted OR of 0.57 (95% CI, 0.35-0.95) for the association between having a dog before the age of 1 year and food and inhalant sensitization in Finnish schoolchildren aged 7 to 16 years. More recent findings from Europe by Marrs et al²¹ demonstrate an even stronger relationship, with an adjusted OR of 0.1 (95% CI, 0.01-0.71) between dog ownership before 3 months and challenge-confirmed FA to cow's milk, egg white, cod, peanut, sesame, and wheat in infants aged 1 to 3 years from the United Kingdom and Wales.²¹ Perhaps the association is stronger depending on how young the subject is at exposure, or depending on how old the subject is when the outcome is measured. Our finding that having a pet dog in childhood was not as strongly inversely associated with FS in adulthood as with FS in childhood, might be explained by the fact that the exposure to dog before the age of 5 years instead of 2 years was examined in adults. Or maybe the protective effect does not last until adulthood. Alternatively, one should consider the fact that the adults stemmed from an environmentally different childhood era than the children in this study, which could mean that predictors for the current adults differ from those for the current children when reaching adulthood.

Previous literature suggests that environmental factors other than having a pet dog in childhood also influence the likelihood of FA.²³⁻²⁶ Two environmental determinants that are relatively consistently suggested to protect against FA in children are an increasing number of siblings, especially older siblings,²³⁻²⁶ and rural or farm lifestyle.^{23,27,28} In our study, these determinants also exhibited an inverse association with FS in univariable analysis, both for children and for adults. However, the suggested protective effects were attenuated and lost statistical significance in multivariable analysis. Although the current study was not specifically powered to detect associations (of minimal relevant size) for all predictors studied, nor was it designed to assess causal associations, our study is unique in that it included both

childhood environmental exposures and infant dietary determinants in multivariable analysis for prediction of childhood FS, which may influence the observed associations in comparison with earlier studies where a more limited set of predictive factors was evaluated. Furthermore, because the outcome FA is often (partly) defined by a measure of subjective interpretation, subjects self-reporting symptoms may be more likely to report risk factors associated with FA than subjects without symptoms, thus possibly inflating associations. Our objective outcome, FS, may have mitigated these associations.

Nonetheless, several studies also report a significant protective effect of early-life farm exposure on IgE sensitization, in both children^{11,29} and adults.^{17,30} All these studies, however, focused on IS. In our study, early-life farm exposure, but also bedroom sharing in childhood for example, was more strongly inversely associated with IS than with FS in both children and adults, to the point of reaching statistical significance. Even larger differences were observed when comparing IS to primary FS. It is possible that predictors for FS and IS differ (in effect size), despite shared pathophysiological mechanisms.

Early-life exposures: Infant diet

Regarding infant diet, none of the dietary determinants evaluated in our study significantly predicted FS in childhood, except for the use of hypoallergenic infant formula. Findings from models with further adjustment for comorbid atopy and IS, where the association between the use of hypoallergenic infant formula and FS lost statistical significance, suggest that reverse causality may play a role here. In other words, food-sensitized infants may be more likely to receive hypoallergenic infant formula rather than the other way around.

Literature is inconsistent on whether breast-feeding is protective against allergy, neutral, or allergy-promoting.³¹ In accordance with our findings, most systematic reviews of literature conclude that there appears to be no significant association between breast-feeding ever versus never, or breast-feeding duration, and FA.^{23,32,33} Interestingly, Hong et al³¹ found that breast-feeding significantly increased or decreased the odds of FS in childhood depending on genotype, implying that individual genes may decide whether breast-feeding promotes or protects against FS.³¹

No significant trend was found for timing of introduction of infant formula or solid foods and likelihood of FS in childhood in multivariable analyses, but effect direction did suggest that earlier introduction of solid foods may protect against FS.

Introduction before 4 months would appear to be associated with the least likely FS, as was also concluded in a recent systematic review and meta-analyses by Burgess et al.³⁴

Demographic characteristics

Demographic factors were taken into account for complete adjustment, and as expected, some were relevant predictors of FS in our data. Interestingly, higher gestational age at delivery was found to be inversely related to FS in childhood. Available literature on the relationship between gestational age and the outcome FS is scarce, and previously showed no significant relationship.³⁵ For the outcome FA, some results are contradictory in that they reveal a positive association between preterm birth and FA,^{19,36} whereas others again report no significant relationship.^{37,38} Several studies suggest that immune system homeostasis, gut barrier function, and diversity in gut microbiota are essential for normal tolerance development.^{39,40} Because these features are underdeveloped in preterm infants, this may make FS more likely. Another possibility is that there is confounding through cesarean section, on which we had no data. Systematic reviews have concluded that cesarean section, which is more common in preterm births, is positively associated with both FS and FA, mostly based on the theory that babies born through cesarean section are deprived of first colonization of the gut with maternal vaginal bacteria.^{39,41}

In adults, FS significantly decreased with age in our study. Our data on primary FS in children suggest the same effect direction for children, but the association probably did not reach statistical significance due to the small age range in included children (7-10 years). Similar trends were found in cross-sectional studies in American, Italian, and German children and adults.⁴²⁻⁴⁴ These trends may be the result of increasing prevalence of FS over time, as suggested by some studies,^{3,6,7} which would lead to a higher prevalence of sensitization in the younger age groups.

Male sex was positively associated with FS in adults. The latter finding appears to contradict the predominating thought that women are at a higher risk of FA than men.^{23,26,32,45} However, with regard to FS, available studies also found that adult males are more likely to be food sensitized than adult females.^{42,44} Because many studies investigate the outcome FA rather than FS, outcome measures are mainly based on patient history. Because women are more likely than men to report symptoms to foods,^{44,46,47} this may explain the discrepancy.

Strengths and limitations

Overall, this study is unique in that data on determinants were analyzed for the outcomes FS, IS, and primary FS, in both children and adults, after assessing IgE sensitization to 24 foods. A limitation is the retrospective data collection on childhood determinants, which means that some recall bias is likely, especially in adults. Also, causal inference was limited, because we had no information on when sensitization developed in relation to the exposure variables. We did attempt to take the possibility of reverse causality into account, assessing the change in associations after adjusting for comorbid atopy. The standardized approach of this multicenter study all across Europe is a major strength, allowing valid comparisons. The broad inclusion from the general population and the use of multiple imputation for sporadically missing data on determinants yielded a large study

population in which we could evaluate most currently conceived environmental, infant dietary, and demographic risk factors.

CONCLUSIONS

Our findings consolidate existing evidence that dog ownership in early childhood protects against FS in later childhood. Other postulated environmental and infant dietary risk factors for FA appear to have (more) limited impact on childhood or adult FS after mutual adjustment, though preventative tendencies were observed for certain early-life exposures, including early introduction of solid foods. Demographic factors also appear relevant, in that gestational age affects the likelihood of childhood FS, and age and sex the likelihood of adult FS.

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ONLINE REPOSITORY

METHODS

Questionnaires

The EuroPrevall phase I screening questionnaire was a self-administered 1-page document, designed to detect subjects with and without food-related reactions. The phase II questionnaire was an extensive interviewer-administered questionnaire on symptoms and potential risk factors for FA (Figures E2 and E3).

Determinants

Data on evaluated childhood environmental determinants were obtained from the phase II questionnaire, and consisted of maternal age at the birth of subject, number of siblings, number of older siblings, bedroom sharing with any sibling and with older siblings, day care attendance, dog or cat ownership, growing up on a farm, growing up in the inner-city, and having serious respiratory infections. In children, antibiotic use before the age of 2 years, use of reflux medication in the previous 6 months, maternal smoking during pregnancy, and maternal and paternal smoking since the birth of the subject (at least 1 cigarette per day) were also investigated. Regarding infant diet, duration of breast-feeding, age of start of infant formula, type of infant formula (cow's milk, soy milk, hypoallergenic), age of introduction of solid foods, and vitamin D supplementation before the age of 2 years were assessed. For adults, environmental determinants later in life were food-related occupation (ever

worked in the growing, production, processing, or distribution of food), smoking (ever for longer than 1 year), and frequency of use of indigestion medication (antacids, H2-antagonists, or proton pump inhibitors).

Demographic factors, consisting of age, sex, and (parental) level of education for all subjects, and gestational age at birth, birth length, and weight for children, were also evaluated.

Food and inhalant allergens

Specific IgE testing was performed in phase II for 24 foods, which are often implicated in FA or frequently consumed across Europe. These foods were hen's egg, cow's milk, fish, shrimp, peanut, hazelnut, walnut, peach, apple, kiwi, melon, banana, tomato, celery, carrot, corn, lentils, soy, wheat, buckwheat, sesame seed, mustard seed, sunflower seed, and poppy seed. They were termed *priority* foods. IgE testing was also performed for 6 common inhalant allergens: birch, mugwort, grass, and parietaria pollen, house-dust mite, and cat.

IgE testing

All serum samples were analyzed in a single laboratory in the Academic Medical Center, Amsterdam, The Netherlands, using commercially available ImmunoCAP tests (Phadia, *currently ThermoFisher Scientific*, Uppsala, Sweden). All sera that tested positive for at least 1 of the priority foods in phase II, and a random sample of nonsensitized controls, were further tested for specific food allergens using an allergen microarray assay.^{E1-E3}

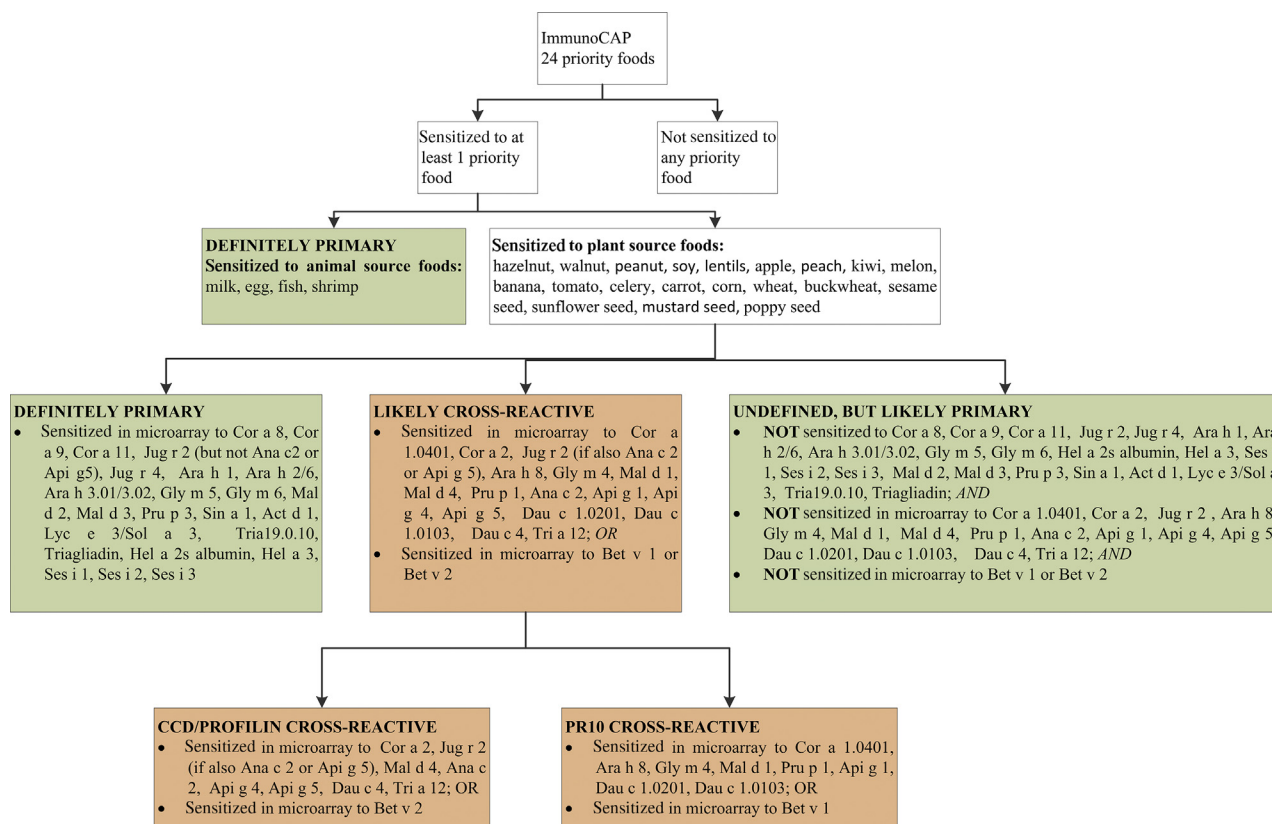


FIGURE E1. Classification of FS into primary sensitization and cross-reactive sensitization. Subjects were classified into 1 or more of the boxes depending on their sensitization patterns (ie, subjects could have both primary and cross-reactive sensitization). This is a simplified classification, designed for exploratory purposes, and subjects with cross-reactive sensitization through food rather than pollen, or with cross-reactive sensitization to tropomyosins (eg, shrimp through house-dust mite), have been classified as primary sensitization. However, aforementioned cross-reactivity patterns are much less common than pollen-related cross-reactivity, and are expected to have only limited influence on the prevalence of primary FS. In the prediction modeling of the outcome primary sensitization, the negative outcome comprised no sensitization, or cross-reactive sensitization only. *CCD*, cross-reactive carbohydrate determinants; *PR-10*, pathogenesis-related protein family 10 proteins. Green: Primary sensitization (= definite, or undefined but likely primary sensitization). Orange: Cross-reactive sensitization.

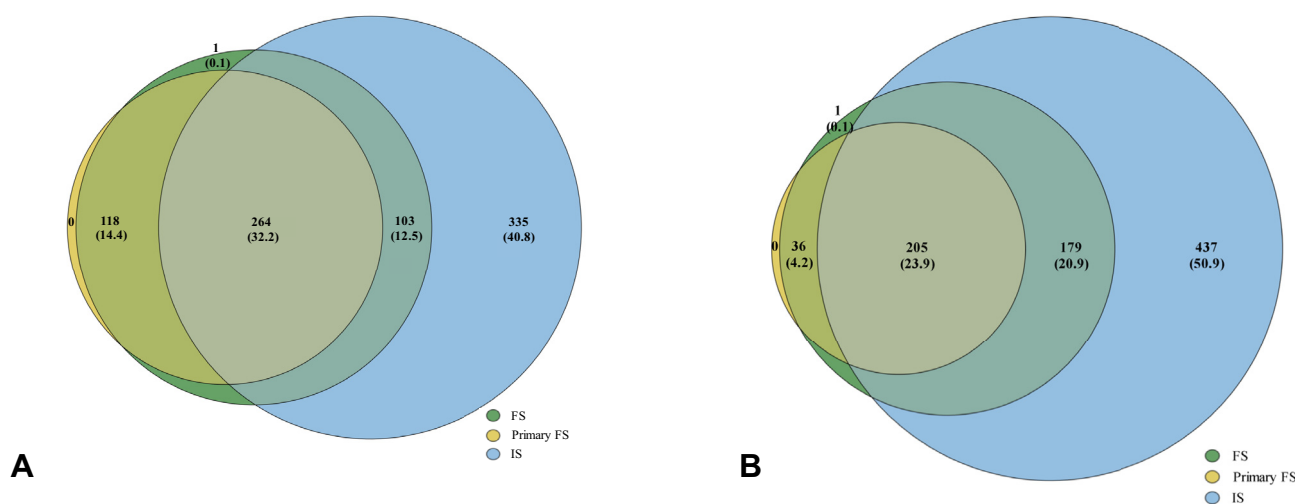


FIGURE E2. Relationship between FS, primary FS, and IS in (A) children and (B) adults. The numbers (%) represent individual subjects included in the study with the particular (combination of) outcome(s). Only subjects with complete data on FS, primary FS, and IS were included in these diagrams.



Child Case-Control Questionnaire

ID Number Today's date
DAY MONTH YEAR
 1. What is this child's date of birth?DAY MONTH YEAR

2. Sex of child

male female
☐ ☐

FOOD ALLERGY

3. Has this child ever had an illness or problem caused by eating any of the following foods? Say whether or not this child avoids them because they make him/her ill, and approximately how often this child eats the following foods:

FOOD	Has this child ever had an illness or problem caused by eating any of the following foods? Tick as many as apply		Does this child avoid this food because it makes him/her ill?		How often does this child eat this food (in season) Tick one column only				
	No	Yes	No	Yes	Most Days	Most weeks	Most months	< Most months	Never
3.1 Cows' milk*									
3.2 Hen's eggs									
3.3 Fish									
3.4 Shrimp/Lobster									
3.5 Other shellfish									
3.6 Peanut									
3.7 Hazelnut									
3.8 Walnut									
3.9 Chocolate									
3.10 Peach									
3.11 Apple									
3.12 Kiwi fruit									
3.13 Bananas									
3.14 Melon									
3.15 Strawberry									
3.16 Orange									
3.17 Tomato									
3.18 Avocado									
3.19 Celery									
3.20 Carrot									
3.21 Soybean									
3.22 Chick pea									
3.23 Lentils									
3.24 Wheat**									
3.25 Buckwheat									
3.26 Corn									
3.27 Rice									
3.28 Sesame seed									
3.29 Mustard seed									
3.30 Sunflower seed									
3.31 Poppy seed									

* Other cow's milk products including butter, cheese, yoghurt, crème fraîche, fromage frais....

** Including wheat products such as bread and breakfast cereals

FIGURE E3. EuroPrevall phase II questionnaire for children.

4. Has this child had any problems eating any **other** food or foods? NO YES
☐ ☐

If yes please list the foods:

4.1 Food _____

CODE
☐ ☐

4.2 Food _____

CODE
☐ ☐

4.3 Food _____

CODE
☐ ☐

**If you have answered 'NO' to questions 3 AND 4 please go to question 5.
If 'YES':**

4.4 Which of all these foods mentioned above gave this child the worst problems? _____

CODE
☐ ☐

4.5 How old was this child when he/she had his/her first problem eating this food?

YEARS
☐ ☐

4.6 How old was this child when he/she had his/her most recent problem eating this food?

YEARS
☐ ☐

4.7 How often has this child had this illness or problem after eating this food?

please tick
one only
Only once ☐
2-4 times ☐
More than 4 times ☐

4.8 Has this child avoided eating this food since his/her illness or problem? NO YES
☐ ☐

4.9 Did this illness or problem include:

4.9.1 Itching, tingling or swelling in the mouth, lips or throat?

4.9.2 A rash, nettle sting like rash or itchy skin?

4.9.3 Diarrhoea or vomiting (other than food poisoning)?

4.9.4 Runny or stuffy nose?

4.9.5 Red, sore or running eyes?

4.9.6 Difficulty swallowing?

4.9.7 Breathlessness?

4.9.8 Stiffness in his/her joints?

4.9.9 Fainting or dizziness?

4.9.10 Headaches?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

4.10 Has this child had any other symptoms when eating this food? NO YES
☐ ☐

If yes, please describe _____

4.11 How long after eating the food did this child start with the first symptom? Minutes: ☐ ☐ Hours: ☐ ☐ Days: ☐

FIGURE E3. Continued

4.12 How long did it last?

Minutes:

--	--

Hours:

--	--

Days:

--

4.13 Did this child receive any treatment?

NO

--

YES

--

If yes, could you tell us the name of any medicine used

4.13.1 Medicine

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

CODE

--	--

4.13.2 Medicine

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

CODE

--	--

4.13.3 Medicine

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

CODE

--	--

5. Have you ever been told by a doctor that this child has a food allergy?

NO

--

YES

--

6. Has this child received vitamin D *as a supplement* in the first two years of life?

NO

--

YES

--

DON'T
KNOW

--

7. Does this child drink milk?

please tick
one only

Yes, mostly full fat milk

--

Yes, mostly half fat milk

--

Yes, mostly low fat milk

--

No

--

8. Does this child eat butter or margarine?

please tick
one only

Yes, mostly butter

--

Yes, mostly margarine

--

No

--

ASTHMA AND ALLERGIES9. Has this child had wheezing or whistling in his/her chest at any time in the last **12 months?**

NO

--

YES

--

If 'NO' go to question 10.**If 'YES':**

9.1 Has this child been at all breathless when the wheezing noise was present?

NO

--

YES

--

9.2. Has this child had this wheezing or whistling when he/she did **not** have a cold?

NO

--

YES

--

10. Has this child ever had asthma?

NO

--

YES

--

If 'NO' go to question 11.

FIGURE E3. Continued

If 'YES':

10.1 How old was this child when he/she had his/her first attack of asthma?

YEARS

10.2 Has this child had an attack of asthma in the last **12 months**?

NO YES
☐ ☐

If 'NO' go to question 11.

If 'YES':

10.3 How many times has this child been woken up because of his/her asthma in the last **12 months**?

Every night or almost every night
More than once a week, but not most nights
At least twice a month, but not more than once a week
Less than twice a month
Not at all

please tick
one only

☐
☐
☐
☐
☐

11. Does this child have any nasal allergies, including hay fever?

NO YES
☐ ☐

If 'NO' go to question 11.2.

If 'YES':

11.1 How old was this child when he/she first had hay fever or nasal allergy?

YEARS

11.2. Has this child ever had a problem with sneezing, or a runny or a blocked nose when he/she did not have a cold or the flu?

NO YES
☐ ☐

If 'NO' go to question 11.4, if 'YES':

11.3. Has this child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu **in the last 12 months**?

NO YES
☐ ☐

If 'NO' go to question 12.

If 'YES':

11.4 Has this nose problem been accompanied by itchy or watery eyes?

NO YES
☐ ☐

12. Has this child **ever** had an itchy rash that was coming and going for at least **6 months**?

NO YES
☐ ☐

If 'NO' go to question 12.2.

If 'YES':

12.1 How old was this child when he/she first had this itchy rash?

YEARS

12.2 Has this child had an itchy rash **at any time** that affected any of the following places:

12.2.1 the folds of the elbows
12.2.2 behind the knees
12.2.3 in front of the ankles
12.2.4 around the neck
12.2.5 around the ears
12.2.6 around the eyes

NO YES
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐

FIGURE E3. Continued

If 'YES' to any of the above:12.3 Has this child had this itchy rash **at any time in the last 12 months?**

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

13. Has this child ever had eczema?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

14. When this child is near animals, such as cat as a dog or a horse, does he/she **ever**

14.1 start to cough?

14.2 start to wheeze?

14.3 get a feeling of tightness in his/her chest?

14.4 start to feel short of breath?

14.5 get a runny or stuffy nose or start to sneeze?

14.6 get itchy or watering eyes?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

15. When this child is near trees, grass or flowers, or when there is a lot of pollen about, does he/she **ever**

15.1 start to cough?

15.2 start to wheeze?

15.3 get a feeling of tightness in his/her chest?

15.4 start to feel short of breath?

15.5 get a runny or stuffy nose or start to sneeze?

15.6 get itchy or watering eyes?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

16. Has this child ever had immunotherapy for allergy?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' or 'DON'T KNOW' go to question 17.**If 'YES':**

16.1 What allergens was he/she desensitised for?

16.1.1 pollen counts

16.1.2 mites

16.1.3 latex

16.1.4 others

16.1.5 I don't know

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

17. Within the last 6 months:

17.1 Has this child vomited when NOT having "winter vomiting disease" or food poisoning?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

17.2 Has this child complained of feelings like vomiting or feeling nauseous when NOT having "winter vomiting disease" or food poisoning?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

17.3 Has this child complained of having a burning or painful feeling in the middle of his/her chest?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

17.4 Has this child, complained of having a sour taste, like the taste of vomit in his/her mouth?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

17.5. **Within the last 6 months**, has this child taken any medications for acid regurgitation /gastroesophageal reflux?

NO YES
☐ ☐

If yes, which medicine was/is it? (including antacids over-the-counter) :

17.5.1 Medicine _____

CODE
☐ ☐

17.5.2 Medicine _____

CODE
☐ ☐

17.5.3 Medicine _____

CODE
☐ ☐

PREGNANCY AND BIRTH OF THIS CHILD

18. How old was the mother when she gave birth to **this child**?

YEARS
☐ ☐

19. At how many weeks of pregnancy was **this child** born?

WEEKS
☐ ☐

20. What was the length of this child when it was born?

CENTIMETERS

21. What was the weight of this child when it was born?

GRAM

22. How many times did this child move house during the **first two years** of his/her life?

None
Once
More than once

please tick
one only
☐
☐
☐

23. What country was this child born in? _____

CODE

IF NOT THIS COUNTRY:

23.1 How old was this child when he/she left the country of his/her birth?

YEARS

24. Did the mother have an alcoholic drink during her pregnancy **of this child**?

NO YES
☐ ☐

If yes, **on average**, how often did the mother have an alcoholic drink during her pregnancy **of this child**?

Once every couple of months
Once or twice a month
Once or twice a week
Three or four days a week
Almost every day

please tick
one only
☐
☐
☐
☐
☐

25. Did the mother smoke during her pregnancy **of this child**?

NO YES
☐ ☐

If yes, **on average** during the time of the pregnancy **of this child**, how much did the mother smoke?

25.1 number of cigarettes per day
25.2 other tobacco in grams / week

INFANT FEEDING

26. Was this child **ever** breastfed?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

Breastfeeding also means expressed breast milk given in a bottle

If 'NO' go to question 27.

If 'YES':

26.1 How old was this child when the breastfeeding was stopped completely?

Days:	<input type="text"/>	<input type="text"/>	Weeks:	<input type="text"/>	<input type="text"/>	Months:	<input type="text"/>	<input type="text"/>
-------	----------------------	----------------------	--------	----------------------	----------------------	---------	----------------------	----------------------

27. Has this child **ever** received any infant formula?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' go to question 28.

If 'YES':

27.1 How old was this child when he/she received the formula for the first time?

Days:	<input type="text"/>	<input type="text"/>	Weeks:	<input type="text"/>	<input type="text"/>	Months:	<input type="text"/>	<input type="text"/>
-------	----------------------	----------------------	--------	----------------------	----------------------	---------	----------------------	----------------------

27.2 How old was this child when feeding the formula was stopped?

Days:	<input type="text"/>	<input type="text"/>	Weeks:	<input type="text"/>	<input type="text"/>	Months:	<input type="text"/>	<input type="text"/>
-------	----------------------	----------------------	--------	----------------------	----------------------	---------	----------------------	----------------------

27.3 Which of the following types of infant formula has this child received?

please tick

27.3.1 Normal cow's milk formula

27.3.2 Normal soy milk formula

27.3.3 Hypo-allergenic (modified) formula

27.3.4 Other (please specify).....

<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

28. At what age were supplemental liquids other than milk and water started?

WEEKS
<input type="text"/>

29. At what age were solid foods started?

WEEKS
<input type="text"/>

OTHER ISSUES RELATED TO HEALTH AND DISEASE

30. Did this child have a serious respiratory infection before the age of two years?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

31. Was this child hospitalised before the age of two years for lung disease?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

32. Was this child ever given antibiotics in the first two years of life?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

FIGURE E3. Continued

YOU AND YOUR HOUSEHOLD

33. How many brothers and sisters does this child have or did have?

NUMBER

--	--

If 'NONE' go to question 34.

If 'YES':

33.1 How many **older** brothers and sisters?

33.2 How many **younger** brothers and sisters?

33.3 How many of the brothers and sisters ever had asthma?

33.4 How many of the brothers and sisters, who **did not** have asthma, ever had other allergies such as eczema or skin allergies, nasal allergy or hay fever?

NUMBER

--	--

34. How many **other** children regularly slept in this child's bedroom before he/she was **two years old**?

CHILDREN

--

35. Did this child regularly share his/her bedroom with any **older** children before the age of two years?

NO YES

--	--

36. Did this child go to a school, play-school or nursery with **older children** before the age of two years?

NO YES

--	--

If 'NO' go to question 37.

If 'YES':

36.1 At what age did this child first attend a school, play school, day care or nursery?

MONTHS

--	--

37. What term best describes the place this child lived most of the time when he/she was under the age of two years?

Farm

Village in a rural area

Small town

Suburb of a city

Inner city

Combination of rural and town/city*

***for example when staying regularly with family at the country site during weekends**

please tick
one only

38. Did anyone in your household keep any of the following pets **in the first two years of life of this child**?

38.1 Cats

38.2 Dogs

38.3 Horses

38.4 Birds

38.5 Guinea pigs or other furry animals

38.6 Other: _____

NO YES

FIGURE E3. Continued

39. Does anyone in your household keep any of the following pets **at this moment**?

- 39.1 Cats
39.2 Dogs
39.3 Horses
39.4 Birds
39.5 Rabbits
39.6 Mice
39.5 Guinea pigs or other furry animals
39.6 Other: _____

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

40. How often is this child present in the kitchen when food is being prepared?

- Most times
Sometimes
Rare
Never

please tick
one only

<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

ABOUT THE MOTHER

41. What country was the mother born in? _____

CODE

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

42. Did the mother ever have a food allergy?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

43. Did the mother ever have asthma?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

44. Did the mother ever have eczema or skin allergy?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

45. Did the mother ever have nasal allergy or hay fever?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

46. What level of education had the mother completed?

- 46.1 Has she completed primary education?
46.2 Has she completed her secondary education?
46.3 Has she been awarded a lower level vocational education diploma?
46.4 Has she been awarded a higher level vocational education diploma?
46.5 Has she been awarded a university degree?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

47. Is the mother currently employed (or self-employed)?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' or 'DON'T KNOW' go to question 48.

If 'YES':

47.1 What is the mother's current or most recent job? [Be as precise as possible]

CODE

--	--	--	--

48. Has the mother ever worked in a job relating to the growing, production, processing or distribution of food?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' or 'DON'T KNOW' go to question 49.

If 'YES':

48.1 What was or is this job? [Be as precise as possible]

CODE

--	--	--	--

DON'T KNOW

--

49. Has the mother ever worked in a job in which she used latex gloves?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' or 'DON'T KNOW' go to question 50.

If 'YES':

49.1. Were these ever powdered latex gloves?

NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

50. Has the mother smoked since the birth of this child?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

'YES' means at least one cigarette per day or one cigar or 360g of tobacco a week

If 'NO' go to question 51.

If 'YES':

50.1 Was the mother smoking when the child was born?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' go to question 50.3.

If 'YES':

50.2. **On average** when the child was born **of this child**, how much did the mother smoke?

50.2.1 number of cigarettes per day

--	--

50.2.2 other tobacco in grams / week

--	--	--

Go to question 50.5

50.3 How old was this child when the mother started smoking (again)?

YEARS

--	--

50.4. **On average** at the time the mother started smoking (again), how much did the mother smoke?

50.4.1 number of cigarettes per day

--	--

50.4.2 other tobacco in grams / week

--	--	--

50.5 **On average** how much does the mother **now** smoke?

50.5.1 number of cigarettes per day

--	--

50.5.2 other tobacco in grams / week

--	--	--

50.5.3 stopped smoking

--

FIGURE E3. Continued

If the mother stopped smoking:

50.6 How old was this child when the mother stopped smoking?

YEARS

--	--

51. How many people in your household smoked regularly in the house ***in the first 2 years of life of this child?******'Regularly' means on most days***

NUMBER

--	--

52. How many hours a day was this child exposed to tobacco smoking ***in the first 2 years of life?***

HOURS

--	--

53. How many people in your household smoke regularly in the house **now?*****'Regularly' means on most days***

NUMBER

--	--

54. How many hours a day is this child exposed to tobacco smoking?

HOURS

--	--

ABOUT THE FATHER

55. What country was the father born in? _____

CODE

--	--	--

56. Did the father ever have a food allergy?

NO	YES	DON'T KNOW

57. Did the father ever have asthma?

NO	YES	DON'T KNOW

58. Did the father ever have eczema or skin allergy?

NO	YES	DON'T KNOW

59. Did the father ever have nasal allergy or hay fever?

NO	YES	DON'T KNOW

60. What level of education had the father completed?

60.1 Has he completed primary education?

60.2 Has he completed his secondary education?

60.3 Has he been awarded a lower level vocational education diploma?

60.4 Has he been awarded a higher level vocational education diploma?

60.5 Has he been awarded a university degree?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

61. Is the father currently employed (or self-employed)?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

If 'NO' go to question 62***If 'YES':***

61.1 What is the father's current or most recent job? [Be as precise as possible]

CODE

--	--	--	--

FIGURE E3. Continued

62. Has the father ever worked in a job relating to the growing, production, processing or distribution of food?

NO YES DON'T
KNOW
☐ ☐ ☐

If 'NO' or 'DON'T KNOW' go to question 63.

If 'YES':

62.1 What was or is this job? [Be as precise as possible]

CODE DON'T
KNOW
☐ ☐ ☐ ☐ ☐

63. Has the father ever worked in a job in which he used latex gloves?

NO YES DON'T
KNOW
☐ ☐ ☐

If 'NO' or 'DON'T KNOW' go to question 64.

If 'YES':

63.1. Were these ever powdered latex gloves?

NO YES DON'T
KNOW
☐ ☐ ☐

64. Has the father smoked since the child was born?

NO YES
☐ ☐

['YES' means at least one cigarette per day or one cigar or 360g of tobacco a week]

If 'NO' go to question 65, if 'YES':

64.1 Was the father smoking when the child was born?

NO YES
☐ ☐

If 'NO' go to question 64.3, if 'YES':

64.2. **On average** when the child was born, how much did the father smoke?

64.2.1 number of cigarettes per day

64.2.2 other tobacco in grams / week

Go to question 64.5

64.3 How old was this child when the father started smoking (again)?

YEARS
☐ ☐

64.4. **On average** at the time the father started smoking (again), how much did he smoke?

64.4.1 number of cigarettes per day

64.4.2 other tobacco in grams / week

64.5 **On average** how much does the father smoke **now**?

64.5.1 number of cigarettes per day

64.5.2 other tobacco in grams / week

64.5.3 stopped smoking

If the father stopped smoking:

64.6 How old was this child when the father stopped smoking?

YEARS
☐ ☐

65. Are you willing to be contacted again for further food allergy studies?

NO YES
☐ ☐

Thank you very much for completing this questionnaire

This questionnaire was administered to:

Mother

Father

Partner of mother/father

Guardian

FIGURE E3. Continued



Adult Case-Control Questionnaire

ID Number

DAY MONTH YEAR
Date

1. What is your date of birth?

DAY MONTH YEAR

2. Are you male or female?

MALE FEMALE
☐ ☐

3. Have you ever had an illness or trouble caused by eating any of the following foods?

Tick as
many as
apply

- | | | |
|------|-------------------|--------------------------|
| 3.1 | Cow's milk* | <input type="checkbox"/> |
| 3.2 | Hen's eggs | <input type="checkbox"/> |
| 3.3 | Fish | <input type="checkbox"/> |
| 3.4 | Shrimp or Lobster | <input type="checkbox"/> |
| 3.5 | Other shellfish | <input type="checkbox"/> |
| 3.6 | Peanut | <input type="checkbox"/> |
| 3.7 | Hazelnut | <input type="checkbox"/> |
| 3.8 | Walnut | <input type="checkbox"/> |
| 3.9 | Chocolate | <input type="checkbox"/> |
| 3.10 | Peach | <input type="checkbox"/> |
| 3.11 | Apple | <input type="checkbox"/> |
| 3.12 | Kiwi fruit | <input type="checkbox"/> |
| 3.13 | Bananas | <input type="checkbox"/> |
| 3.14 | Melon | <input type="checkbox"/> |
| 3.15 | Strawberry | <input type="checkbox"/> |
| 3.16 | Orange | <input type="checkbox"/> |
| 3.17 | Tomato | <input type="checkbox"/> |
| 3.18 | Avocado | <input type="checkbox"/> |
| 3.19 | Celery | <input type="checkbox"/> |
| 3.20 | Carrot | <input type="checkbox"/> |
| 3.21 | Soybean | <input type="checkbox"/> |
| 3.22 | Chick pea | <input type="checkbox"/> |
| 3.23 | Lentils | <input type="checkbox"/> |
| 3.24 | Wheat** | <input type="checkbox"/> |
| 3.25 | Buckwheat | <input type="checkbox"/> |
| 3.26 | Corn | <input type="checkbox"/> |
| 3.27 | Rice | <input type="checkbox"/> |
| 3.28 | Sesame seed | <input type="checkbox"/> |
| 3.29 | Mustard seed | <input type="checkbox"/> |
| 3.30 | Sunflower seed | <input type="checkbox"/> |
| 3.31 | Poppy seed | <input type="checkbox"/> |

* Other cow's milk products including butter, cheese, yoghurt, crème fraîche, fromage frais....

** Including wheat products such as bread and breakfast cereals

FIGURE E4. EuroPrevall phase II questionnaire for adults.

4. Have you had any problems eating any other food or foods? If yes please list the foods:

4.1 Food _____

CODE

--	--

4.2 Food _____

CODE

--	--

4.3 Food _____

CODE

--	--

**If you have answered 'NO' to questions 3 AND 4 please go to question 5.
If 'YES':**

4.4 Which of all these foods gave you the worst problems? _____

CODE

--	--

4.5 How old were you when you had your first problem eating this food?

YEARS

--	--

4.6 How old were you when you had your most recent problem eating this food?

YEARS

--	--

4.7 How often have you had this illness or trouble after eating this food?

please tick

Only once

2-4 times

More than 4 times

--

--

--

4.8. Have you avoided eating this food since your illness or trouble?

NO

YES

--

--

4.9 Did this illness or trouble include:

4.9.1. Itching, tingling or swelling in the mouth, lips or throat?

4.9.2. A rash, nettle sting like rash or itchy skin?

4.9.3. Diarrhoea or vomiting (other than food poisoning)?

4.9.4. Runny or stuffy nose?

4.9.5. Red, sore or running eyes?

4.9.6. Difficulty swallowing?

4.9.7. Breathlessness?

4.9.8. Stiffness in your joints?

4.9.9. Fainting or dizziness?

4.9.10. Headaches?

NO

YES

--

--

--

--

--

--

--

--

--

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--

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--

--

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--

--

--

--

4.10. Have you had any other symptoms?

NO

YES

--

--

If yes, please describe _____

4.11. How long after eating the food did you start with the first symptom?

Minutes:

--

Hours:

--

Days:

--

4.12. How long did it last?

Minutes:

--	--

Hours:

--	--

Days:

--

FIGURE E4. Continued

4.13. Did you receive any treatment? NO ☐ YES ☐

If yes, could you tell us the name of any medicine used

4.13.1 Medicine _____

CODE

4.13.2 Medicine _____

CODE

4.13.3 Medicine _____

CODE

4.14. Have you ever been told by a doctor that you have a food allergy? NO ☐ YES ☐

5. Say approximately how often you eat the following foods, and whether or not you avoid them because they make you ill:

FOOD	Do you avoid this food because it makes you ill?		How often do you eat this food (in season) Tick one column only				
	No	Yes	Most Days	Most weeks	Most months	< Most months	Never
1 Cow's milk*							
2 Hen's eggs							
3 Fish							
4 Shrimp/Lobster							
5 Other shellfish							
6 Peanut							
7 Hazelnut							
8 Walnut							
9 Chocolate							
10 Peach							
11 Apple							
12 Kiwi fruit							
13 Bananas							
14 Melon							
15 Strawberry							
16 Orange							
17 Tomato							
18 Avocado							
19 Celery							
20 Carrot							
21 Soybean							
22 Chick pea							
23 Lentils							
24 Wheat**							
25 Buckwheat							
26 Corn							
27 Rice							
28 Sesame seed							
29 Mustard seed							
30 Sunflower seed							
31 Poppy seed							

* Other cow's milk products including butter, cheese, yoghurt, crème fraîche, fromage frais....

** Including wheat products such as bread and breakfast cereals

FIGURE E4. Continued

ASTHMA AND ALLERGIES

6. Have you had wheezing or whistling in your chest at any time in the last **12 months?**

NO YES
☐ ☐

IF 'NO' GO TO QUESTION 7, IF 'YES':

6.1 Have you been at all breathless when the wheezing noise was present?

NO YES
☐ ☐

6.2. Have you had this wheezing or whistling when you did **not** have a cold?

NO YES
☐ ☐

7. Have you ever had asthma?

NO YES
☐ ☐

IF 'NO' GO TO QUESTION 8, IF 'YES':

7.1 Was this confirmed by a doctor?

NO YES
☐ ☐
YEARS

7.2 How old were you when you had your first attack of asthma?

YEARS

7.3 How old were you when you had your most recent attack of asthma?

7.4. Which months of the year do you usually have attacks of asthma?

7.4.1 January / February

7.4.2 March / April

7.4.3 May / June

7.4.4 July / August

7.4.5 September / October

7.4.6 November / December

NO YES
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐

7.5 Have you ever been admitted to hospital with an attack of asthma?

NO YES
☐ ☐

7.6 Have you had an attack of asthma in the last **12 months?**

NO YES
☐ ☐

IF NO GO TO Q8, IF YES

7.6.1 How many attacks of asthma have you had in the last **12 months?**

ATTACKS

ATTACKS

7.6.2 How many attacks of asthma have you had in the last **3 months?**

7.7 How many times have you been woken up because of your asthma in the last **3 months?**

TICK ONE BOX ONLY

Every night or almost every night

More than once a week, but not most nights

At least twice a month, but not more than once a week

Less than twice a month

Not at all

☐ 1
☐ 2
☐ 3
☐ 4
☐ 5

7.8 How often have you had trouble with your breathing because of your asthma in the last **3 months?**

TICK ONE BOX ONLY

Continuously

☐ 1

FIGURE E4. Continued

About once a day	<input type="checkbox"/>	2
At least once a week, but less than once a day	<input type="checkbox"/>	3
Less than once a week	<input type="checkbox"/>	4
Not at all	<input type="checkbox"/>	5

8. Do you have any nasal allergies, including hay fever?

IF NO GO TO Q9, IF YES

8.1 How old were you when you first had hay fever or nasal allergy?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
YEARS	
<input type="text"/>	<input type="text"/>

9. Have you ever had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu?

IF NO GO TO Q10, IF YES

9.1. Have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu **in the last 12 months?**

IF NO GO TO Q10, IF YES

9.1.1. Has this nose problem been accompanied by itchy or watery eyes?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

9.1.2. In which months of the year did this nose problem occur?

9.1.2.1 January/ February	NO	YES
9.1.2.2 March/ April	<input type="checkbox"/>	<input type="checkbox"/>
9.1.2.3 May/ June	<input type="checkbox"/>	<input type="checkbox"/>
9.1.2.4 July/ August	<input type="checkbox"/>	<input type="checkbox"/>
9.1.2.5 September/ October	<input type="checkbox"/>	<input type="checkbox"/>
9.1.2.6 November/ December	<input type="checkbox"/>	<input type="checkbox"/>

10. Have you **ever** had an itchy rash that was coming and going for at least **6 months?**

IF NO GO TO Q11, IF YES

10.1 How old were you when you first had this itchy rash?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
YEARS	
<input type="text"/>	<input type="text"/>

10.2. Have you had this itchy rash **in the last 12 months?**

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

11. Have you had an itchy rash **at any time** that affected any of the following places:

11.1.1 the folds of the elbows	NO	YES
11.1.2 behind the knees	<input type="checkbox"/>	<input type="checkbox"/>
11.1.3 in front of the ankles	<input type="checkbox"/>	<input type="checkbox"/>
11.1.4 around the neck	<input type="checkbox"/>	<input type="checkbox"/>
11.1.5 around the ears	<input type="checkbox"/>	<input type="checkbox"/>
11.1.6 around the eyes	<input type="checkbox"/>	<input type="checkbox"/>

IF 'YES' TO ANY OF THE ABOVE:

11.2 Have you had this itchy rash **in the last 12 months?**

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

12. When you are near animals, such as cats, dogs or horses, do you **ever**

12.1 start to cough?	NO	YES
12.2 start to wheeze?	<input type="checkbox"/>	<input type="checkbox"/>
12.3 get a feeling of tightness in your chest?	<input type="checkbox"/>	<input type="checkbox"/>
12.4 start to feel short of breath?	<input type="checkbox"/>	<input type="checkbox"/>
12.5 get a runny or stuffy nose or start to sneeze?	<input type="checkbox"/>	<input type="checkbox"/>

FIGURE E4. Continued

12.6 get itchy or watering eyes? ☐ ☐

13. When you are near trees, grass or flowers, or when there is a lot of pollen about, do you **ever**

	NO	YES
13.1 start to cough?	<input type="checkbox"/>	<input type="checkbox"/>
13.2 start to wheeze?	<input type="checkbox"/>	<input type="checkbox"/>
13.3 get a feeling of tightness in your chest?	<input type="checkbox"/>	<input type="checkbox"/>
13.4 start to feel short of breath?	<input type="checkbox"/>	<input type="checkbox"/>
13.5 get a runny or stuffy nose or start to sneeze?	<input type="checkbox"/>	<input type="checkbox"/>
13.6 get itchy or watering eyes?	<input type="checkbox"/>	<input type="checkbox"/>

IF 'YES' TO ANY OF THE ABOVE:

13.7 Which time of year does this happen?

	NO	YES
13.7.1 winter	<input type="checkbox"/>	<input type="checkbox"/>
13.7.2 spring	<input type="checkbox"/>	<input type="checkbox"/>
13.7.3 summer	<input type="checkbox"/>	<input type="checkbox"/>
13.7.4 autumn	<input type="checkbox"/>	<input type="checkbox"/>

14. After taking any medicines (including antibiotics) have you ever had any of the following

	NO	YES
14.1.1 Itching, tingling or swelling in the mouth, lips or throat?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.2 A rash, nettle sting like rash or itchy skin?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.3 Diarrhoea or vomiting ?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.4 Runny or stuffy nose?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.5 Red, sore or running eyes?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.6 Difficulty swallowing?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.7 Breathlessness?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.8 Stiffness in your joints?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.9 Fainting or dizziness?	<input type="checkbox"/>	<input type="checkbox"/>
14.1.10 Headaches?	<input type="checkbox"/>	<input type="checkbox"/>

14.2 Have you had any other symptoms after taking medicines?

	NO	YES
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14.2.1 If yes, please describe _____

14.3 Do you remember what medicine this was?

	CODE
14.3.1 Medicine _____	<input type="checkbox"/> <input type="checkbox"/>
14.3.2 Medicine _____	<input type="checkbox"/> <input type="checkbox"/>
14.3.3 Medicine _____	<input type="checkbox"/> <input type="checkbox"/>

15. Have you ever had immunotherapy for allergy?

	NO	YES	DON'T KNOW
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 16, IF 'YES':

15.1 If YES, what allergens were you immunised against?

Tick as many as apply

15.1.1 Pollens	<input type="checkbox"/>
15.1.2 Mites	<input type="checkbox"/>
15.1.3 Latex	<input type="checkbox"/>
15.1.4 Other	<input type="checkbox"/>

FIGURE E4. Continued

15.1.5 Unknown

☐

15.2 How old were you when you first had immunotherapy?

YEARS	
<input type="text"/>	<input type="text"/>

15.3 How old were you when you last had immunotherapy?

YEARS	
<input type="text"/>	<input type="text"/>

15.4 Was the immunotherapy

- a) By injection?
b) Under your tongue?
c) Other?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

INDIGESTION

16. How often do you get any of the following symptoms?

	Never	<1/ year	<1/ month	<1/ week	1-2/ week	3-5/ week	every day
16.1 Regurgitating stomach contents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.2 Burning sensation behind the breastbone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.3 Acid taste in the mouth	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.4 Have you woken with any of these symptoms?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never	<1/ year	<1/ month	<1/ week	1-2/ week	3-5/ week	every day
16.5 How often do you take medicine bought without prescription for indigestion?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.6 How often do you take medicine prescribed by your doctor for indigestion?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

IF 'NEVER' GO TO QUESTION 17, otherwise

16.7 Which medicine was/is this?

16.7.1 Medicine _____	CODE <input type="text"/> <input type="text"/>
16.7.2 Medicine _____	CODE <input type="text"/> <input type="text"/>
16.7.3 Medicine _____	CODE <input type="text"/> <input type="text"/>

16.8 How old were you when you first started taking any regular treatment for indigestion?

YEARS	
<input type="text"/>	<input type="text"/>

16.9 Have you taken any medicine prescribed by your doctor for indigestion in the last 3 months?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

16.10 Have you ever had an operation to cure or help your indigestion?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

SMOKING

17. Have you ever smoked for as long as a year?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

['YES' means at least one cigarette per day or one cigar a week for one year or 360g of tobacco]

FIGURE E4. Continued

IF 'NO' GO TO QUESTION 18, IF 'YES':

17.1 How old were you when you started smoking?

YEARS	
NO	YES

17.2 Do you **now** smoke, as of **one month ago**?

IF 'NO' GO TO QUESTION 17.3, IF 'YES':

How much do you **now** smoke on average?

17.2.1 number of cigarettes per day

17.2.2 number of cigarillos per day

17.2.3 number of cigars a week

17.2.4 pipe tobacco in grams / week

NUMBER	
NO	YES

17.3 Have you stopped or cut down smoking?

IF 'NO' GO TO QUESTION 17.4 IF 'YES':

17.3.1 how old were you when you stopped or cut down smoking?

YEARS	

17.3.2 **on average** of the entire time you smoked, before you stopped or cut down, how much did you smoke?

17.3.2.1 number of cigarettes per day

17.3.2.2 number of cigarillos per day

17.3.2.3 number of cigars a week

17.3.2.4 pipe tobacco in grams / week

NUMBER	
NO	YES

17.4 Do you or did you inhale the smoke?

ALCOHOL

18. Please read the following statements carefully and tick the box next to the one that best describes you:

18.1.1 I have never tasted an alcoholic drink

18.1.2 I have tasted alcohol once or twice, but never had a whole drink

18.1.3 I have had a proper alcoholic drink – a whole drink not just a taste

TICK ONE ONLY	

18.2 How old were you the first time you had a proper alcoholic drink?

YEARS	

18.3 How often do you usually have an alcoholic drink:

Less than once a year

Once or twice a year

Once every couple of months

Once or twice a month

Once or twice a week

Three or four days a week

Five or six days a week

Almost every day

TICK ONE ONLY	

18.4 How much of the following have you drunk in the last seven days:

FIGURE E4. Continued

- 18.4.1 Draught Beer, Lager or Cider
 18.4.2 Beer, Lager or Cider
 18.4.3 Beer, Lager or Cider
 18.4.4 Measures of spirits (doubles count as 2) e.g. gin, vodka, whisky, rum
 18.4.5 Fortified wine (e.g. sherry, martini, port, vermouth, cinzano, dubonnet)
 18.4.6 Wine (125ml glasses)
 18.4.7 Other (specify) _____

		Litres/Pints
		330ml cans/bottles
		660ml cans/bottles
		measures
		measures
		125 ml glasses

YOUR FAMILY

19.1 How many brothers and sisters do or did you have?

NUMBER	DON'T KNOW
<input type="text"/>	<input type="text"/>

IF 'NONE' GO TO QUESTION 20.1, IF 'YES':

19.2.1 How many **older** brothers and sisters?19.2.2 How many **younger** brothers and sisters?

19.2.3 How many of your brothers and sisters ever had asthma?

19.2.4 How many of your brothers and sisters, who **did not** have asthma, ever had other allergies such as eczema or skin allergies, nasal allergy or hay fever?

NUMBER	DON'T KNOW
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>

19.3 Did your mother ever have asthma?

NO	YES	DON'T KNOW
<input type="text"/>	<input type="text"/>	<input type="text"/>

19.4 Did your mother ever have eczema, skin or nasal allergy or hay fever?

NO	YES	DON'T KNOW
<input type="text"/>	<input type="text"/>	<input type="text"/>

19.5 Did your father ever have asthma?

NO	YES	DON'T KNOW
<input type="text"/>	<input type="text"/>	<input type="text"/>

19.6 Did your father ever have eczema, skin or nasal allergy or hay fever?

NO	YES	DON'T KNOW
<input type="text"/>	<input type="text"/>	<input type="text"/>

EDUCATION AND WORK

20.1 Are you a full time student?

NO	YES
<input type="text"/>	<input type="text"/>

IF 'YES' GO TO QUESTION 20.3, IF 'NO':

20.2 At what age did you complete full time education?

YEARS
<input type="text"/>

20.3 What level of education have you completed?

NO	YES
<input type="text"/>	<input type="text"/>

FIGURE E4. Continued

- 20.3.1 Have you completed primary education?
20.3.2 Have you completed your secondary education?
20.3.3 Have you been awarded a lower level vocational education diploma?
20.3.4 Have you been awarded a higher level vocational education diploma?
20.3.5 Have you been awarded a university degree

- 20.4 Are you currently employed (or self-employed)?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

IF 'YES' GO TO QUESTION 20.5, IF 'NO':

- 20.4.1 Are you currently looking for a job?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

- 20.5 What is your current or most recent job? [Be as precise as possible]

CODE			

- 20.6 Are you or were you

- a) a manager working for an employer?
b) a foreman or supervisor working for an employer?
c) working for an employer, but neither a manager, supervisor or foreman?
d) self-employed?

TICK ONE BOX ONLY	
1	<input type="checkbox"/>
2	<input type="checkbox"/>
3	<input type="checkbox"/>
4	<input type="checkbox"/>

21. Have you ever worked in a job relating to the growing, production, processing or distribution of food?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>

IF 'NO' GO TO QUESTION 21.2 IF 'YES':

- 21.1 How old were you when you first did this type of job?

YEARS	
<input type="text"/>	<input type="text"/>

- 21.1.1 What was or is this job? [Be as precise as possible]

CODE			

- 21.1.2 Does/did this involve

- a) growing or production?
b) processing?
c) distribution?

NO	YES
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

- 21.1.3 What foods were involved?

CODE		

- 21.2 To what extent are you involved with food preparation at home?

- a) Have nothing to do with food preparation
b) Sometimes present in the kitchen when food is being prepared
c) Occasionally prepare and cook food in the kitchen
d) Prepare and cook food in the kitchen at least once a week
e) Prepare and cook food in the kitchen on most days

TICK ONE BOX ONLY	
1	<input type="checkbox"/>
2	<input type="checkbox"/>
3	<input type="checkbox"/>
4	<input type="checkbox"/>
5	<input type="checkbox"/>

FIGURE E4. Continued

21.3 Have you ever worked in a job in which you used latex gloves?
IF NO, go to question 22; IF YES
 21.12 How old were you when you first did this type of job?

NO YES
☐ ☐
 YEARS

 NO YES
☐ ☐

21.12.1 Were these ever powdered latex gloves?

22. YOUR CHILDHOOD

22.1 How old was your mother when you were born?

YEARS

22.2 What country were you born in? _____

CODE

IF NOT THIS COUNTRY:

22.2.1 How old were you when you left the country of your birth?

YEARS

22.3. How many times did you move house during the first five years of your life?

None
 Once
 more than once

TICK ONE BOX ONLY

1 ☐
 2 ☐
 3 ☐

22.4 What term best describes the place you lived most of the time when you were under the age of five years?

a) farm
 b) village in a rural area
 c) small town
 d) suburb of a city
 e) inner city

TICK ONE BOX ONLY

1 ☐
 2 ☐
 3 ☐
 4 ☐
 5 ☐

22.5 When you were a child did anyone in your household keep any of the following pets?

22.5.1 cats
 22.5.2 dogs
 22.5.3 horses
 22.5.4 birds
 22.5.5 guinea pigs or other furry animals
 22.5.6 other: _____

NO YES
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐

22.6 How many **other** children regularly slept in your bedroom before you were **five years old**?

CHILDREN

22.7 Did you regularly share your bedroom with any **older** children before the age of five years?

NO YES DON'T KNOW
☐ ☐ ☐

22.8 Did you go to a school, play-school or nursery with **older** children before the age of five years?

NO YES DON'T KNOW
☐ ☐ ☐

22.9 At what age did you first attend a school, play school, day care or nursery?

YEARS

22.10 Did you have a serious respiratory infection before the age of five years?

NO YES DON'T KNOW
☐ ☐ ☐

22.11 Were you hospitalised before the age of two years for lung disease?

NO YES
☐ ☐

23. Are you willing to be contacted again for further food allergy studies?

NO YES
☐ ☐

Thank you very much for completing this questionnaire

FIGURE E4. Continued

TABLE E1. Amount of missing data in predictor variables

Predictor variable	Children (N = 2196)	Adults (N = 2185)
Demographic characteristic		
Age	0	0
Sex	0	0
Level of education	0	0
Gestational age	26	NA
Birth weight	31	NA
Birth length	76	NA
Childhood environment		
Maternal age	7	5
No. of siblings	6	9
No. of older siblings	6	9
Bedroom sharing with any sibling	6	2
Bedroom sharing with older children	2	11
Day care attendance	2	58
Farm environment	0	0
Inner-city environment	0	0
Pet dog	1	0
Pet cat	1	0
Serious respiratory tract infection	1	186
Use of antibiotics	2	NA
Maternal smoking during pregnancy	3	NA
Maternal smoking since birth	2	NA
Paternal smoking since birth	2	NA
Reflux medication in last 6 mo	0	NA
Infant diet		
Vitamin D supplementation	123	NA
Breast-feeding duration	30	NA
Cow's milk infant formula	22	NA
Soy milk infant formula	26	NA
Hypoallergenic infant formula	25	NA
Age start infant formula	31	NA
Age introduction solid foods	50	NA
Adult environment		
Smoking	NA	0
Food-related work	NA	0
Indigestion medication	NA	0
Variables for model adjustment		
Comorbid atopy	50	103
Parental FA	233	NA
Sensitization to pollen	32	44
Sensitization to HDM or cat	32	44
Primary FS	1	0
Center	0	0

HDM, House-dust mite; NA, not available.

Values for these missing data were estimated using multiple imputation procedures, for which all the above determinants were included as covariates, along with the outcome FS.

TABLE E2. Comparison of subjects with and without available food serology

Variable	Children			Adults		
	Food serology available (N = 2196)	Food serology missing (N = 130)	P	Food serology available (N = 2185)	Food serology missing (N = 71)	P
Age (y), mean \pm SD	8.9 \pm 1.0	8.9 \pm 0.9	.937	38.3 \pm 9.6	38.1 \pm 9.0	.842
Sex						
Male	1096 (49.9)	61 (46.9)	.508	932 (42.7)	20 (28.2)	.015
Female	1100 (50.1)	69 (53.1)		1253 (57.3)	51 (71.8)	
Highest level of education (parents)						
High	938 (42.7)	61 (46.9)	.348	1436 (65.7)	44 (62.0)	.513
Low	1257 (57.3)	61 (46.9)		749 (34.3)	27 (38.0)	
Allergic asthma	416 (18.9)	22 (16.9)	.567	323 (14.8)	6 (8.5)	.137
Allergic rhinitis	710 (32.3)	43 (33.1)	.860	1093 (50.0)	34 (47.9)	.810
Atopic dermatitis	833 (37.9)	56 (43.1)	.241	393 (18.0)	10 (14.1)	.398
Family atopy	1732 (81.9)	102 (81.6)	.935	1411 (73.7)	36 (63.2)	.075
Parental FA	505 (25.7)	31 (27.0)	.769	NA	NA	NA
Symptoms to any foods	917 (41.8)	53 (40.8)	.824	1121 (51.3)	31 (43.7)	.205
Symptoms to priority foods	661 (30.1)	30 (23.1)	.089	744 (34.1)	18 (25.4)	.127
Center						
Zurich	304 (13.8)	26 (20.0)	<.001	482 (22.1)	22 (31.0)	<.001
Madrid	278 (12.7)	22 (16.9)		309 (14.1)	5 (7.0)	
Athens	155 (7.1)	27 (20.8)		67 (3.1)	35 (49.3)	
Utrecht	398 (18.1)	23 (18.5)		476 (21.8)	4 (5.6)	
Lodz	453 (20.6)	6 (4.6)		378 (17.3)	5 (7.0)	
Reykjavik	457 (20.8)	12 (9.2)		473 (21.6)	0 (0.0)	
Vilnius	151 (6.9)	13 (10.0)		NA	NA	

NA, Not available.

Results presented in n (%) unless otherwise specified. Bold indicates statistical significance ($P < .05$).

TABLE E3. Comparison of model III to model III adjusted for comorbid atopy and IS

Variable	Model III				Model III + comorbid atopy*				Model III + comorbid atopy + IS†			
	Children		Adults		Children		Adults		Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Demographic characteristic												
Age (y)	1.01 (0.91-1.13)	.85	0.97 (0.96-0.98)	<.001	1.02 (0.90-1.16)	.85	0.97(0.96-0.99)	<.001	0.96 (0.84-1.10)	.55	0.99 (0.97-1.01)	.21
Male sex	1.01 (0.82-1.25)	.92	1.39 (1.12-1.73)	<.001	1.01 (0.79-1.28)	.81	1.45 (1.16-1.81)	<.001	0.64 (0.49-0.84)	<.001	1.34 (1.01-1.77)	.04
High level of education‡	1.02 (0.80-1.29)	.88	0.86 (0.67-1.09)	.21	1.02 (0.79-1.36)	>.99	0.84 (0.65-1.07)	.16	0.96 (0.72-1.29)	.80	0.76 (0.56-1.04)	.09
Gestational age (wk)	0.93 (0.87-0.99)	.01	NA	NA	0.93 (0.88-0.99)	.02	NA	NA	0.92 (0.86-0.99)	.03	NA	NA
Birth length (cm)	1.00 (1.00-1.00)	.97	NA	NA	1.01 (0.96-1.05)	.71	NA	NA	1.01 (0.96-1.06)	.75	NA	NA
Birth weight (g)	1.01 (0.97-1.06)	.65	NA	NA	1.00 (1.00-1.00)	.93	NA	NA	1.00 (1.00-1.00)	.85	NA	NA
Childhood environment												
Maternal age (y)	0.99 (0.97-1.01)	.33	1.01 (0.99-1.03)	.45	0.99 (0.96-1.01)	.32	1.01 (0.98-1.03)	.50	0.99 (0.96-1.02)	.46	1.00 (0.97-1.03)	.98
No. of siblings												
1	0.86 (0.63-1.18)	.28	1.22 (0.75-1.97)	.74	0.85 (0.62-1.17)	.36	1.38 (0.85-2.23)	.50	1.03 (0.70-1.51)	.89	0.92 (0.50-1.69)	.51
2	1.09 (0.73-1.64)		1.34 (0.78-2.29)		1.06 (0.71-1.59)		1.52 (0.89-2.61)		1.04 (0.63-1.73)		1.25 (0.63-2.47)	
3 or more	0.76 (0.40-1.44)		1.35 (0.75-2.42)		0.77 (0.40-1.47)		1.49 (0.83-2.68)		0.80 (0.36-1.76)		1.15 (0.55-2.41)	
No. of older siblings												
1	0.85 (0.63-1.15)	.62	1.17 (0.85-1.62)	.75	0.86 (0.64-1.16)	.65	1.17 (0.84-1.61)	.77	0.89 (0.62-1.28)	.70	1.56 (1.04-2.35)	.18
2	1.02 (0.63-1.18)		1.21 (0.78-1.88)		1.02 (0.63-1.65)		1.21 (0.78-1.88)		1.21 (0.67-2.18)		1.34 (0.76-2.35)	
3 or more	0.77 (0.31-1.95)		1.22 (0.69-2.14)		0.75 (0.29-1.90)		1.20 (0.68-2.11)		1.06 (0.35-3.17)		1.23 (0.60-2.54)	
Bedroom sharing with other children	0.77 (0.53-1.13)§	.18	0.84 (0.62-1.14)	.26	0.76 (0.51-1.11)§	.15	0.84 (0.62-1.13)	.25	1.02 (0.63-1.63)§	.95	0.95 (0.65-1.40)	.79
Bedroom sharing with older children	1.19 (0.79-1.80)§	.40	0.75 (0.52-1.06)	.11	1.21 (0.80-1.83)§	.37	0.77 (0.54-1.10)	.14	1.08 (0.65-1.79)§	.78	0.76 (0.48-1.19)	.23
Day care attendance	0.82 (0.64-1.05)§	.12	1.02 (0.80-1.30)	.89	0.82 (0.64-1.06)§	.13	1.01 (0.54-1.10)	.97	0.84 (0.62-1.13)§	.24	1.10 (0.80-1.50)	.56
Farm environment	1.06 (0.21-5.36)§	.95	0.73 (0.40-1.35)	.32	1.09 (0.21-5.56)§	.92	0.75 (0.40-1.39)	.35	1.76 (0.27-11.39)§	.55	1.15 (0.53-2.51)	.72
Inner-city environment	0.94 (0.76-1.17)§	.60	1.01 (0.79-1.29)	.93	0.96 (0.77-1.19)§	.69	0.97 (0.76-1.25)	.84	1.02 (0.79-1.34)§	.86	1.09 (0.79-1.50)	.60
Pet dog	0.65 (0.48-0.90)	.01	0.94 (0.70-1.27)	.61	0.65 (0.47-0.89)§	.01	0.94 (0.74-1.21)	.65	0.81 (0.55-1.18)§	.27	1.12 (0.82-1.52)	.48
Pet cat	1.04 (0.77-1.40)§	.79	0.87 (0.68-1.10)	.24	1.02 (0.76-1.38)§	.89	0.89 (0.70-1.13)	.35	1.26 (0.88-1.80)§	.21	1.06 (0.78-1.43)	.71
Serious respiratory tract infection	1.11 (0.86-1.45)§	.42	0.88 (0.62-1.25)	.47	1.10 (0.84-1.43)§	.50	0.86 (0.60-1.23)	.40	1.33 (0.96-1.83)§	.09	0.90 (0.58-1.41)	.66
Use of antibiotics	1.14 (0.89-1.45)§	.29	NA	NA	1.10 (0.86-1.40)§	.46	NA	NA	1.07 (0.79-1.43)§	.67	NA	NA
Maternal smoking during pregnancy	0.74 (0.51-1.08)	.12	NA	NA	0.74 (0.51-1.07)	.11	NA	NA	0.71 (0.45-1.13)	.15	NA	NA
Maternal smoking since birth	1.12 (0.84-1.48)	.45	NA	NA	1.13 (0.85-1.50)	.41	NA	NA	1.35 (0.95-1.91)	.09	NA	NA
Paternal smoking since birth	0.97 (0.77-1.22)	.78	NA	NA	0.97 (0.77-1.23)	.82	NA	NA	0.86 (0.65-1.13)	.27	NA	NA
Reflux medication in last 6 mo	0.61 (0.17-2.19)	.45	NA	NA	0.56 (0.16-2.02)	.38	NA	NA	0.70 (0.15-3.30)	.65	NA	NA
Infant diet												
Vitamin D supplementation	1.05 (0.75-1.47)§	.77	NA	NA	1.03 (0.74-1.45)§	.85	NA	NA	1.01 (0.67-1.53)§	.96	NA	NA

(continued)

TABLE E3. (Continued)

Variable	Model III				Model III + comorbid atopy*				Model III + comorbid atopy + IS†			
	Children		Adults		Children		Adults		Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Breast-feeding duration												
≤4 mo	1.20 (0.82-1.75)	.29	NA	NA	1.17 (0.80-1.72)	.40	NA	NA	1.30 (0.81-2.08)	.27	NA	NA
4-6 mo	1.20 (0.75-1.94)		NA	NA	1.19 (0.74-1.93)	.28	NA	NA	1.28 (0.71-2.31)	.61	NA	NA
>6 mo	0.91 (0.57-1.46)		NA	NA	0.89 (0.55-1.42)		NA	NA	1.11 (0.62-1.97)		NA	NA
Cow's milk infant formula	0.85 (0.58-1.24)	.39	NA	NA	0.83 (0.57-1.21)		NA	NA	0.77 (0.48-1.23)		NA	NA
Soy milk infant formula	1.35 (0.89-2.05)	.16	NA	NA	1.29 (0.84-1.96)	.23	NA	NA	1.17 (0.69-1.98)	.56	NA	NA
Hypoallergenic infant formula	1.51 (1.06-2.15)	.02	NA	NA	1.44 (1.01-2.05)	.04	NA	NA	1.27 (0.82-1.96)	.29	NA	NA
Age start infant formula												
0-4 mo	1.02 (0.60-1.72)	.33	NA	NA	1.05 (0.62-1.77)	.31	NA	NA	1.31 (0.70-2.48)	.59	NA	NA
4-6 mo	1.04 (0.60-1.79)		NA	NA	1.05 (0.61-1.82)		NA	NA	1.25 (0.64-2.45)		NA	NA
6-11 mo	1.10 (0.66-1.82)		NA	NA	1.12 (0.67-1.86)		NA	NA	1.55 (0.82-2.91)		NA	NA
≥11 mo	1.79 (0.94-3.40)		NA	NA	1.84 (0.97-3.51)		NA	NA	1.73 (0.78-3.84)		NA	NA
Age introduction solid foods												
4-6 mo	1.37 (1.00-1.86)	.19	NA	NA	1.39 (1.02-1.89)	.17	NA	NA	1.18 (0.81-1.71)	.82	NA	NA
6-11 mo	1.22 (0.86-1.71)		NA	NA	1.22 (0.87-1.72)		NA	NA	1.12 (0.75-1.69)		NA	NA
≥11 mo	1.45 (0.93-2.27)		NA	NA	1.43 (0.92-2.24)		NA	NA	1.07 (0.61-1.86)		NA	NA
Adult environment												
Smoking	NA	NA	0.99 (0.79-1.24)	.94	NA	NA	1.03 (0.82-1.29)	.81	NA	NA	1.20 (0.90-1.61)	.22
Food-related occupation	NA	NA	0.83 (0.64-1.07)	.15	NA	NA	0.80 (0.62-1.05)	.11	NA	NA	0.80 (0.57-1.11)	.18
Indigestion medication currently												
Yes, <1×/mo	NA	NA	1.30 (0.85-1.97)	.59	NA	NA	1.21 (0.79-1.85)	.63	NA	NA	1.43 (0.84-2.44)	.16
Yes, <1×/wk	NA	NA	1.10 (0.46-2.60)		NA	NA	1.01 (0.42-2.42)		NA	NA	1.06 (0.35-3.20)	
Yes, ≥ 1×/wk	NA	NA	0.84 (0.46-1.54)		NA	NA	0.76 (0.41-1.41)		NA	NA	1.17 (0.56-2.42)	
Other allergy												
Comorbid atopy	NA	NA	NA	NA	2.02 (1.30-3.15)	<.001	3.55 (2.22-5.66)	<.001	1.40 (0.85-2.30)	.18	1.60 (0.92-2.79)	.10
Parental FA	NA	NA	NA	NA	1.12 (0.87-1.44)	.37	NA	NA	0.89 (0.65-1.21)	.46	NA	NA
Positive serology to pollen	NA	NA	NA	NA	NA	NA	NA	NA	13.15 (9.92-17.44)	<.001	13.10 (9.67-17.74)	<.001
Positive serology to HDM or cat	NA	NA	NA	NA	NA	NA	NA	NA	2.79 (2.08-3.74)	<.001	5.35 (3.96-7.22)	<.001

HDM, House-dust mite; NA, not available.

Bold indicates statistical significance ($P < .05$). Analyses were adjusted for center. P values for continuous variables (age, gestational age, birth weight, birth length, and maternal age) were based on the 2-sample t test, and those for categorical variables on the χ^2 test.

Reference categories: "number of (older) siblings" = 0; "indigestion medication" = no or <1×/y; "breast-feeding duration" = never; "age start infant formula" = never; "age introduction solid food" = 0-4 mo.

*This model was adjusted for comorbid atopy (asthma, allergic rhinitis, or atopic dermatitis in subject or first-degree family member).

†This model was adjusted for comorbid atopy and IS (specific IgE against birch, grass, mugwort, parietaria, HDM, or cat). All P values for continuous variables (age, gestational age, birth weight, birth length, and maternal age) were based on the 2-sample t test, and those for categorical variables on the χ^2 test.

‡For children: high level of education of parents.

§Before the age of 2 y.

||Before the age of 5 y.

TABLE E4. Predictors for FS compared with predictors for IS and primary FS

Variable	FS				IS				Primary FS			
	Children		Adults		Children		Adults		Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Demographic characteristic												
Age (y)	1.01 (0.91-1.13)	.85	0.97 (0.96-0.98)	<.001	1.11 (1.00-1.22)	.05	0.96 (0.95-0.97)	<.001	1.00 (0.88-1.12)	.93	0.96 (0.95-0.98)	<.001
Male sex	1.01 (0.82-1.25)	.92	1.39 (1.12-1.73)	<.001	1.62 (1.34-1.96)	<.001	1.39 (1.16-1.68)	<.001	0.99 (0.79-1.25)	.93	1.46 (1.10-1.92)	.01
High level of education*	1.02 (0.80-1.29)	.88	0.86 (0.67-1.09)	.21	1.10 (0.89-1.36)	.40	0.99 (0.80-1.22)	.932	0.93 (0.72-1.20)	.59	0.89 (0.66-1.21)	.47
Gestational age (wk)	0.93 (0.87-0.99)	.01	NA	NA	0.96 (0.91-1.02)	.15	NA	NA	0.96 (0.90-1.02)	.16	NA	NA
Birth weight (g)	1.00 (1.00-1.00)	.97	NA	NA	1.00 (1.00-1.00)	.15	NA	NA	1.00 (1.00-1.00)	.57	NA	NA
Birth length (cm)	1.01 (0.97-1.06)	.65	NA	NA	0.99 (0.97-1.02)	.52	NA	NA	1.02 (0.97-1.07)	.43	NA	NA
Childhood environment												
Maternal age (y)	0.99 (0.97-1.01)	.33	1.01 (0.99-1.03)	.45	0.99 (0.97-1.02)	.61	1.02 (1.00-1.04)	0.03	0.99 (0.97-1.02)	.46	1.01 (0.98-1.04)	.66
No. of siblings												
1	0.86 (0.63-1.18)	.28	1.22 (0.75-1.97)	.74	0.87 (0.66-1.16)	.16	1.50 (1.01-2.25)	.22	0.91 (0.65-1.28)	.29	1.20 (0.65-2.23)	.78
2	1.09 (0.73-1.64)		1.34 (0.78-2.29)		1.18 (0.82-1.70)		1.37 (0.87-2.16)		1.22 (0.79-1.89)		1.40 (0.70-2.78)	
3 or more	0.76 (0.40-1.44)		1.35 (0.75-2.42)		0.93 (0.53-1.63)		1.51 (0.93-2.47)		0.87 (0.43-1.73)		1.30 (0.61-2.79)	
No. of older siblings												
1	0.85 (0.63-1.15)	.62	1.17 (0.85-1.62)	.75	0.92 (0.71-1.20)	.76	0.85 (0.65-1.12)	.63	0.85 (0.61-1.17)	.79	1.47 (0.99-2.18)	.19
2	1.02 (0.63-1.18)		1.21 (0.78-1.88)		0.81 (0.53-1.26)		0.95 (0.66-1.38)		0.91 (0.54-1.52)		1.22 (0.70-2.13)	
3 or more	0.77 (0.31-1.95)		1.22 (0.69-2.14)		0.99 (0.47-2.10)		0.84 (0.53-1.34)		0.90 (0.34-2.35)		1.73 (0.86-3.46)	
Bedroom sharing with other children	0.77 (0.53-1.13) [†]	.18	0.84 (0.62-1.14) [‡]	.26	0.66 (0.46-0.95)[†]	.02	0.81 (0.62-1.04) [‡]	.10	0.88 (0.59-1.33) [†]	.54	1.03 (0.70-1.50) [‡]	.89
Bedroom sharing with older children	1.19 (0.79-1.80) [†]	.40	0.75 (0.52-1.06) [‡]	.11	1.19 (0.81-1.74) [†]	.37	0.86 (0.64-1.16) [‡]	.32	1.14 (0.73-1.77) [†]	.56	0.62 (0.41-0.96)[‡]	.03
Day care attendance	0.82 (0.64-1.05) [†]	.12	1.02 (0.80-1.30) [‡]	.89	0.95 (0.76-1.18) [†]	.63	0.90 (0.73-1.11) [‡]	.35	0.88 (0.68-1.15) [†]	.36	0.91 (0.67-1.24) [‡]	.57
Farm environment	1.06 (0.21-5.36) [†]	.95	0.73 (0.40-1.35) [‡]	.32	0.22 (0.03-1.88) [†]	.17	0.43 (0.25-0.73)[‡]	<.001	1.48 (0.30-7.47) [†]	.63	0.90 (0.44-1.84) [‡]	.77
Inner-city environment	0.94 (0.76-1.17) [†]	.60	1.01 (0.79-1.29) [‡]	.93	0.88 (0.72-1.07) [†]	.20	0.84 (0.68-1.04) [‡]	.11	0.96 (0.76-1.22) [†]	.76	1.17 (0.86-1.59) [‡]	.32
Pet dog	0.65 (0.48-0.90)[†]	.01	0.94 (0.70-1.27) [‡]	.61	0.73 (0.56-0.96)[†]	.02	0.95 (0.77-1.18) [‡]	.66	0.68 (0.48-0.96)[†]	.03	1.02 (0.75-1.40) [‡]	.88
Pet cat	1.04 (0.77-1.40) [†]	.79	0.87 (0.68-1.10) [‡]	.24	0.91 (0.70-1.19) [†]	.50	0.80 (0.65-0.98)[‡]	.03	0.98 (0.71-1.36) [†]	.92	1.02 (0.76-1.38) [‡]	.88
Serious respiratory tract infection	1.11 (0.86-1.45) [†]	.42	0.88 (0.62-1.25) [‡]	.47	0.81 (0.63-1.03) [†]	.08	0.94 (0.70-1.27) [‡]	.71	1.16 (0.87-1.54) [†]	.30	1.37 (0.91-2.05) [‡]	.13
Use of antibiotics	1.14 (0.89-1.45) [†]	.29	NA	NA	1.08 (0.87-1.35) [†]	.46	NA	NA	1.12 (0.86-1.45) [†]	.40	NA	NA
Maternal smoking during pregnancy	0.74 (0.51-1.08)	.12	NA	NA	0.87 (0.62-1.22)	.42	NA	NA	0.85 (0.57-1.27)	.43	NA	NA
Maternal smoking since birth	1.12 (0.84-1.48)	.45	NA	NA	0.86 (0.66-1.11)	.24	NA	NA	1.06 (0.78-1.44)	.73	NA	NA
Paternal smoking since birth	0.97 (0.77-1.22)	.78	NA	NA	1.11 (0.90-1.36)	.33	NA	NA	0.95 (0.74-1.22)	.69	NA	NA
Reflux medication in last 6 mo	0.61 (0.17-2.19)	.45	NA	NA	0.63 (0.20-2.00)	.43	NA	NA	0.85 (0.24-3.05)	.81	NA	NA

(continued)

TABLE E4. (Continued)

Variable	FS				IS				Primary FS			
	Children		Adults		Children		Adults		Children		Adults	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Infant diet												
Vitamin D supplementation	1.05 (0.75-1.47) [†]	.77	NA	NA	0.95 (0.70-1.29) [†]	.74	NA	NA	0.99 (0.69-1.42) [†]	.96	NA	NA
Breast-feeding duration												
≤4 mo	1.20 (0.82-1.75)	.29	NA	NA	1.24 (0.88-1.75)	.23	NA	NA	1.14 (0.75-1.72)	.54	NA	NA
4-6 mo	1.20 (0.75-1.94)		NA	NA	1.43 (0.93-2.21)		NA	NA	1.34 (0.81-2.23)		NA	NA
>6 mo	0.91 (0.57-1.46)		NA	NA	1.10 (0.72-1.68)		NA	NA	1.06 (0.64-1.75)		NA	NA
Cow's milk infant formula	0.85 (0.58-1.24)	.39	NA	NA	1.08 (0.76-1.53)	.68	NA	NA	0.94 (0.63-1.42)	.78	NA	NA
Soy milk infant formula	1.35 (0.89-2.05)	.16	NA	NA	1.27 (0.86-1.87)	.23	NA	NA	1.35 (0.86-2.13)	.19	NA	NA
Hypoallergenic infant formula	1.51 (1.06-2.15)	.02	NA	NA	1.62 (1.17-2.25)	<.001	NA	NA	1.44 (0.98-2.11)	.06	NA	NA
Age start infant formula												
0-4 mo	1.02 (0.60-1.72)	.33	NA	NA	0.83 (0.52-1.33)	.08	NA	NA	1.06 (0.61-1.86)	.93	NA	NA
4-6 mo	1.04 (0.60-1.79)		NA	NA	0.69 (0.42-1.15)		NA	NA	1.04 (0.58-1.88)		NA	NA
6-11 mo	1.10 (0.66-1.82)		NA	NA	0.70 (0.44-1.10)		NA	NA	1.10 (0.63-1.90)		NA	NA
≥11 mo	1.79 (0.94-3.40)		NA	NA	1.31 (0.74-2.33)		NA	NA	1.32 (0.64-2.71)		NA	NA
Age introduction solid foods												
4-6 mo	1.37 (1.00-1.86)	.19	NA	NA	1.34 (1.02-1.76)	.09	NA	NA	1.30 (0.93-1.81)	.30	NA	NA
6-11 mo	1.22 (0.86-1.71)		NA	NA	1.23 (0.91-1.66)		NA	NA	1.16 (0.80-1.68)		NA	NA
≥11 mo	1.45 (0.93-2.27)		NA	NA	1.58 (1.05-2.38)		NA	NA	1.31 (0.81-2.13)		NA	NA
Adult environment												
Smoking	NA	NA	0.99 (0.79-1.24)	.94	NA	NA	0.89 (0.74-1.08)	.24	NA	NA	1.35 (1.01-1.80)	.04
Food-related occupation	NA	NA	0.83 (0.64-1.07)	.15	NA	NA	0.97 (0.78-1.21)	.80	NA	NA	0.77 (0.55-1.08)	.13
Indigestion medication currently												
Yes, <1×/mo	NA	NA	1.30 (0.85-1.97)	.59	NA	NA	1.05 (0.72-1.52)	.91	NA	NA	1.75 (1.09-2.82)	.09
Yes, <1×/wk	NA	NA	1.10 (0.46-2.60)		NA	NA	1.10 (0.53-2.28)		NA	NA	1.77 (0.71-4.47)	
Yes, ≥1×/wk	NA	NA	0.84 (0.46-1.54)		NA	NA	0.87 (0.54-1.40)		NA	NA	1.21 (0.62-2.35)	

NA, Not available.

Bold indicates statistical significance ($P < .05$). Analyses were adjusted for center. P values for continuous variables (age, gestational age, birth weight, birth length, and maternal age) were based on the 2-sample t test, and those for categorical variables on the χ^2 test.

Reference categories: "number of (older) siblings" = 0; "indigestion medication" = no or <1×/y; "breast-feeding duration" = never; "age start infant formula" = never; "age introduction solid food" = 0-4 mo.

*For children: high level of education of parents.

[†]Before the age of 2 y.

[‡]Before the age of 5 y.

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